DERIVATIVES OF 3-AMINOCARBONYLQUINOLINE, PHARMACEUTICAL COMPOSITIONS CONTAINING THEM AND PROCESSES AND INTERMEDIATES FOR THEIR PREPARATION

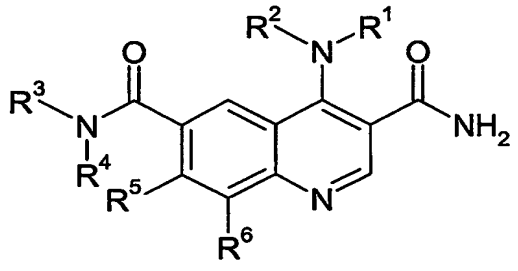
The present invention relates to quinoline compounds, processes for their preparation, intermediates usable in these processes, and pharmaceutical compositions containing the compounds. The invention also relates to the use of the quinoline compounds in therapy, for example as inhibitors of phosphodiesterases and/or for the treatment and/or prophylaxis of inflammatory and/or allergic diseases such as chronic obstructive pulmonary disease (COPD), asthma, rheumatoid arthritis or allergic rhinitis.

WO 02/20489 A2 (Bristol-Myers-Squibb Company) discloses 4-aminoquinoline derivatives wherein the 4-amino group NR^4R^5 may represent an acyclic amino group wherein R^4 and R^5 may each independently represent hydrogen, alkyl, cycloalkyl, aryl, heteroaryl etc.; NR^4R^5 may alternatively represent an aliphatic heterocyclic group. The compounds are disclosed as inhibitors of cGMP phosphodiesterase, especially type 5 (PDE5).

EP 0 480 052 (Otsuka Pharmaceutical Co. Ltd.) discloses 4-aminoquinoline-3-carboxamides wherein the 4-amino group NHR^4 may represent an amino group wherein R^4 represents phenyl, tetrahydronaphthyl or naphthyl, optionally substituted with alkyl, halogen, alkoxy etc.; and the 3-carboxamide group $CONR^2R^3$ represents a primary, secondary or tertiary carboxamide group. The compounds are disclosed as inhibitors of gastric acid secretion, and as cytoprotective agents; inhibition of the ATPase activated by H^+ and K^+ at the gastric wall cells is also disclosed.

It is desirable to find new compounds which bind to, and preferably inhibit, phosphodiesterase type IV (PDE4).

According to the invention there is provided a compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is

Aryl optionally substituted by one or more substituents selected from the group consisting of: C_{1-6} alkoxy, halogen, -CN, C_{1-6} alkyl optionally substituted by one or more halogens, -OH, and C_{1-6} alkylCO;

Heteroaryl optionally substituted by C_{1-3} alkyl;

C_{3-7} cycloalkyl;

Heterocyclyl; or

Aryl fused to a heterocyclyl ring;

R^2 is hydrogen or C_{1-6} alkyl;

R^3 is

Hydrogen;

C_{1-6} alkyl optionally substituted by one or more substituents selected from the group consisting of: heterocyclyl (itself optionally substituted by C_{1-6} alkyl), R^7R^8NCO-, R^9CONR^{10}-, C_{1-6} alkoxy, $R^{11}R^{12}N$-, and C_{1-3} alkyl sulfonyl;

C_{3-7} cycloalkyl;

Aryl$(CH_2)_m$- wherein the aryl is optionally substituted by one or more substituents selected from the group consisting of: halogen and C_{1-6} alkoxy;

Aryl fused to a heterocyclyl ring;

Aryl fused to a C_{4-7} cycloalkyl wherein the cycloalkyl is optionally susbstituted by =O;

Heteroaryl$(CH_2)_m$- wherein the heteroaryl is optionally substituted by one or more substituents selected from the group consisting of: C_{1-6} alkyl, halogen and C_{1-6} alkoxy;

Heterocyclyl$(CH_2)_m$- wherein the heterocyclyl is optionally substituted by one or more substituents selected from the group consisting of: C_{1-6} alkylCO, C_{1-6} alkyl;

R^4 is hydrogen or C_{1-6} alkyl;

R^3 and R^4 together with the nitrogen atom to which they are attached may form a heterocyclyl ring, which is optionally substituted by one or more substituents selected from the group consisting of: C_{1-6} alkylCO, C_{1-6}alkoxy, C_{3-7}cycloalkyl, OH, halogen, C_{1-6} alkyl, $-(CH_2)_mNR^{13}R^{14}$, $-(CH_2)_mCONR^{15}R^{16}$, $-(CH_2)_mNR^{17}COR^{18}$, heteroaryl, heteroarylC_{1-4}alkyl, heteroarylCO, $-CO_2C_{1-6}$alkyl and C_{1-6}alkoxyC_{1-4}alkyl;

R^5 is hydrogen or C_{1-6} alkyl;

R^6 is hydrogen, C_{1-6} alkyl, C_{1-6}alkoxy, fluorine, chlorine, or bromine;;

m is 0-6;

R^{7-18} all independently represent hydrogen, C_{1-6} alkyl;

R^7 and R^8 together with the nitrogen atom to which they are attached may form a heterocyclyl ring;

R^{11} and R^{12} together with the nitrogen atom to which they are attached may form a heterocyclyl ring;

R^{13} and R^{14} together with the nitrogen atom to which they are attached may form a heterocyclyl ring.

As used herein, the term "alkyl" refers to straight or branched hydrocarbon chains containing the specified number of carbon atoms. For example, C_{1-6}alkyl means a straight or branched alkyl chain containing at least 1, and at most 6, carbon atoms. Examples of "alkyl" as used herein include, but are not limited to, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *t*-butyl, *n*-pentyl and *n*-hexyl. A C_{1-4}alkyl group is preferred, for example methyl, ethyl or isopropyl. The said alkyl groups may be optionally substituted with one or more fluorine atoms, for example, trifluoromethyl.

As used herein, the term "alkoxy" refers to a straight or branched chain alkoxy group, for example, methoxy, ethoxy, prop-1-oxy, prop-2-oxy, but-1-oxy, but-2-oxy, 2-methylprop-1-oxy, 2-methylprop-2-oxy, pentoxy or hexyloxy. A C_{1-4}alkoxy group is preferred, for example methoxy or ethoxy. The said alkoxy groups may be optionally substituted with one or more fluorine atoms, for example, trifluoromethoxy.

As used herein, the term "cycloalkyl" refers to a non-aromatic hydrocarbon ring containing the specified number of carbon atoms. For example, C_{3-7}cycloalkyl means a non-aromatic ring containing at least three, and at most seven, ring carbon atoms. Examples of "cycloalkyl" as used herein include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. A C_{3-6}cycloalkyl group is preferred, for example cyclopentyl.

When used herein, the term "aryl" refers to, unless otherwise defined, a mono- or bicyclic carbocyclic aromatic ring system containing up to 10 carbon atoms in the ring system, for instance phenyl or naphthyl, optionally fused to a C_{4-7}cycloalkyl or heterocyclyl ring.

As used herein, the terms "heteroaryl ring" and "heteroaryl" refer to a monocyclic five- to seven- membered heterocyclic aromatic ring containing one or more heteroatoms selected from oxygen, nitrogen and sulfur. In a particular aspect such a ring contains 1-3 heteroatoms. Preferably, the heteroaryl ring has five or six ring atoms. Examples of heteroaryl rings include, but are not limited to, furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, imidazolyl, pyrazolyl, oxadiazolyl, triazolyl, tetrazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl and triazinyl. The terms "heteroaryl ring" and "heteroaryl" also refer to fused bicyclic heterocyclic aromatic ring systems containing at least one heteroatom selected from oxygen, nitrogen and sulfur. Preferably, the fused rings each have five or six ring atoms. Examples of fused heterocyclic aromatic rings include, but are not limited to, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, cinnolinyl, naphthyridinyl, indolyl, indazolyl, pyrrolopyridinyl, benzofuranyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzoxadiazolyl and benzothiadiazolyl. The heteroaryl may attach to the rest of the molecule through any atom with a free valence.

As used herein, the term "heterocyclyl" refers to a monocyclic three- to seven-membered saturated or non-aromatic, unsaturated ring containing at least one heteroatom selected from oxygen, nitrogen and sulfur. In a particular aspect such a ring contains 1 or 2 heteroatoms. Preferably, the heterocyclyl ring has five or six ring atoms. Examples of heterocyclyl groups include, but are not limited to, aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, imidazolidinyl, pyrazolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, diazepinyl, azepinyl, tetrahydrofuranyl, tetrahydropyranyl, and 1,4-dioxanyl.

As used herein, the terms "halogen" or "halo" refer to fluorine, chlorine, bromine and iodine. Preferred halogens are fluorine, chlorine and bromine. Particularly preferred halogens are fluorine and chlorine.

As used herein, the term "optionally" means that the subsequently described event(s) may or may not occur, and includes both event(s) which occur and events that do not occur.

As used herein, the term "substituted" refers to substitution with the named substituent or substituents, multiple degrees of substitution being allowed unless otherwise stated.

In one embodiment of the invention R^1 is

Aryl optionally substituted by one or more C_{1-6}alkoxy groups;

R^2 is hydrogen or C_{1-6} alkyl;

R^3 is

Hydrogen;

C_{1-6} alkyl optionally substituted by one or more substituents selected from: heterocyclyl (itself optionally substituted by C_{1-6} alkyl), R^7R^8NCO-, R^9CONR^{10}-, C_{1-6}alkoxy, $R^{11}R^{12}N$-;

C_{3-7}cycloalkyl;

Aryl or aryl(C_{1-6}alkyl) wherein the aryl is optionally substituted by one or more substituents selected from: halogen, C_{1-6}alkoxy;

Aryl fused to a heterocyclyl ring;

Aryl fused to C_{4-7}cycloalkyl, wherein the cycloalkyl is optionally substituted by =O;

Heteroaryl or heteroaryl(C_{1-6}alkyl), wherein the heteroaryl is optionally substituted by one or more substituents selected from C_{1-6}alkyl, C_{1-6}alkoxy, halogen;

Heterocyclyl or heterocyclyl(C_{1-6}alkyl), wherein the heterocyclyl is optionally substituted by one or more C_{1-6}alkylCO, C_{1-6}alkyl;

R^4 is hydrogen or C_{1-6} alkyl;

R^3 and R^4 together with the nitrogen atom to which they are attached may form a heterocyclyl ring, which is optionally substituted by one or more substituents selected from C_{1-6}alkyl, C_{1-6}alkoxy, C_{3-7}cycloalkyl, C_{1-6}alkylCO, OH, $-(CH_2)_mNR^{13}R^{14}$,

$-(CH_2)_mCONR^{15}R^{16}$, $-(CH_2)_mNR^{17}COR^{18}$, C_{1-6}alkoxyC_{1-4}alkyl, heteroaryl, heteroarylC_{1-4}alkyl, heteroarylCO.

m is 0-6

R^5 is hydrogen or C_{1-6} alkyl;

R^6 is hydrogen, C_{1-6} alkyl, C_{1-6}alkoxy, fluorine, chlorine, or bromine;

R^{7-18} all independently represent hydrogen, C_{1-6} alkyl;

R^7 and R^8 together with the nitrogen atom to which they are attached may form a heterocyclyl ring;

R^{11} and R^{12} together with the nitrogen atom to which they are attached may form a heterocyclyl ring;

R^{13} and R^{14} together with the nitrogen atom to which they are attached may form a heterocyclyl ring.

In another embodiment of the invention R^1 is

Aryl optionally substituted by one or more substituents selected from the group consisting of: C_{1-6} alkoxy, halogen, -CN, C_{1-6} alkyl optionally substituted by one or more halogens, -OH, and C_{1-6} alkylCO;

Heteroaryl optionally substituted by C_{1-3} alkyl;

C_{3-7} cycloalkyl;

Heterocyclyl; or

Aryl fused to a heterocyclyl ring;

R^2 is hydrogen;

R^3 is

Hydrogen;

C_{1-6} alkyl optionally substituted by one or more substituents selected from the group consisting of: C_{1-3} alkoxy and C_{1-3} alkyl sulfonyl;

C_{3-7} cycloalkyl;

Aryl$(CH_2)_m$- wherein the aryl is optionally substituted by one or more substituents selected from the group consisting of: halogen and C_{1-3} alkoxy;

Aryl fused to a heterocyclyl ring;

Aryl fused to a C_{4-7} cycloalkyl wherein the cycloalkyl is optionally substituted by =O;

Heteroaryl$(CH_2)_m$- wherein the heteroaryl is optionally substituted by one or more substituents selected from the group consisting of: C_{1-6} alkyl, halogen and C_{1-6} alkoxy;

Heterocyclyl$(CH_2)_m$- wherein the heterocyclyl is optionally substituted by C_{1-6} alkyl;

R^4 is hydrogen or C_{1-6} alkyl;

R^3 and R^4 together with the nitrogen atom to which they are attached may form a heterocyclyl ring, which is optionally substituted by one or more substituents selected from the group consisting of: C_{1-6} alkylCO, halogen, C_{1-6} alkyl, $-(CH_2)_mNR^{13}R^{14}$, $-CO_2C_{1-6}$alkyl and C_{1-3}alkoxyC_{1-3}alkyl;

R^5 is hydrogen;

R^6 is hydrogen or C_{1-6} alkyl;

m is 0-6;

R^{13} and R^{14} are independently selected from C_{1-6} alkyl.

In a preferred embodiment R^1 is selected from

Phenyl substituted by one or more substituents selected from the group consisting of: methoxy, halogen, methyl, trifluoromethyl, -OH and C_{1-3} alkylCO;

Heteroaryl optionally substituted by methyl;

Phenyl fused to a heterocyclyl ring.

In a preferred embodiment, R^1 is 3-methoxyphenyl.

In a preferred embodiment, R^1 is
2,3-dihydro-1-benzofuran-4-yl, 4-fluoro-3-(methyloxy)phenyl or 1-methyl-1H-indazol-6-yl .

Representative examples of R^1 include:
3-(methyloxy)phenyl, 2,3-dihydro-1-benzofuran-4-yl, 3-methylphenyl, 3-fluorophenyl, 3-chlorophenyl, 4-fluoro-3-methoxyphenyl, cyclohexyl, tetrahydro-2H-pyran-3-yl, 3-(trifluoromethyl)phenyl, 3-hydroxyphenyl, 3-pyridinyl, 3-cyanophenyl, 1-methyl-1H-indazol-6-yl and 3-acetylphenyl.

In a preferred embodiment, R^2 is hydrogen.

Representative examples of R^2 include hydrogen.

In a preferred embodiment R^3 is selected from
C_{1-6} alkyl;

Aryl optionally substituted by one or more substituents selected from: halogen, C_{1-6}alkoxy;

Aryl fused to a heterocyclyl ring;

Aryl fused to cycloalkyl, wherein the cycloalkyl is optionally substituted by =O;

Heteroaryl or heteroaryl(C_{1-6}alkyl), wherein the heteroaryl is optionally substituted by one or more substituents selected from C_{1-6}alkyl, C_{1-6}alkoxy, halogen.

In a preferred embodiment R^3 is selected from:
Hydrogen;

C_{1-4} alkyl optionally substituted by methoxy or methylsulfonyl;

C_{4-6} cycloalkyl;

Phenyl substituted by one or more substituents selected from halogen or methoxy;

Phenyl fused to a 5 membered heterocyclyl ring containing 1 or 2 oxygen atoms;

Phenyl fused to a C_{4-7} cycloalkyl, wherein the cycloalkyl is substituted by =O;

Heteroaryl$(CH_2)_m$- wherein the heteroaryl is optionally substituted by methyl, methoxy or halogen

Heterocyclyl$(CH_2)_m$- wherein the heterocyclyl contains either five or six atoms including one or two heteroatoms selected from nitrogen or oxygen and wherein the heterocyclyl is optionally substituted by C_{1-2} alkyl.

In a preferred embodiment R^3 is selected from:

C_{1-4} alkyl optionally substituted by methoxy or methylsulphonyl;

Pyridyl$(CH_2)_m$-;

Methylpyrazolyl;

Tetrahydropyranyl.

Representative examples of R^3 include:

Hydrogen, phenyl, benzyl, tert-butyl, methyl, 1,3-benzothiazol-6-yl, 2-pyridinylmethyl, 1-methyl-1H-benzimidazol-5-yl, 4-pyridinyl, 3-chlorophenyl, 3-pyridinyl, 3-(methyloxy)phenyl, 4-fluorophenyl, 1,3-benzodioxol-5-yl, 3-oxo-2,3-dihydro-1*H*-inden-5-yl, (1-ethyl-2-pyrrolidinyl)methyl, tetrahydro-2-furanylmethyl, 6-(methyloxy)-3-pyridinyl, 1-methyl-1*H*-pyrazol-5-yl, 2-(4-morpholinyl)ethyl, tetrahydro-2*H*-pyran-4-yl, 2-furanylmethyl, (4-pyridinyl)methyl, 2-(1-pyrrolidinyl)ethyl, 2-(methylsulphonyl)ethyl, 2-(methyloxy)ethyl, (5-chloro-2-pyridinyl)methyl, (3-methyl-5-isoxazolyl)methyl, 1,3-dihydro-2-benzofuran-5-yl, (1,3-thiazol-2-yl)methyl, 4-(methyloxy)phenyl, 1-methyl-4-piperidinyl, 4-chlorophenyl, (1-methyl-1H-imidazol-5-yl)methyl, (1H-tetrazol-5-yl)methyl, 2,3-dihydro-1-benzofuran-4-yl and cyclopentyl.

In a preferred embodiment R^4 is hydrogen or methyl.

In a preferred embodiment R^3 and R^4 together with the nitrogen atom to which they are attached may form a five or six membered heterocyclyl ring, which is optionally substituted by one or more substituents selected from the group consisting of: acetyl, fluoro, methyl, $-N(CH_3)_2$, $-CO_2C_{1-2}$alkyl and C_{1-3}alkoxyC_{1-3}alkyl.

In a preferred embodiment R^3 and R^4 together with the nitrogen atom to which they are attached form a morpholinyl, a 2,6-dimethyl-4-morpholinyl, a 3-(ethoxycarbonyl)-1-piperidinyl, a 4-(*N,N*-dimethylamino)1-piperidinyl, a 4-acetyl-1-piperazinyl or a 4-[(2-methyloxy)ethyl]-1-piperazinyl ring.

In a more preferred embodiment, R^3 and R^4 together with the nitrogen atom to which they are attached may form a heterocyclyl ring, optionally substituted by C_{1-6}alkylCO.

In a particularly preferred embodiment R^3 and R^4 together with the nitrogen to which they are attached represent 4-morpholinyl or 1-piperidinyl.

Representative examples wherein R^3 and R^4 together with the nitrogen atom to which they are attached may form a heterocyclyl ring include 4-morpholinyl, 4-acetyl-1-piperazinyl, 1-pyrrolidinyl, 1-piperidinyl, 4,4-difluoro-1-piperidinyl, 4-(*N,N*-dimethylamino)-1-piperidinyl, 3-(ethoxycarbonyl)-1-piperidinyl, 4-[(2-methyloxy)ethyl]-1-piperazinyl, and 2,6-dimethyl-4-morpholinyl.

In a preferred embodiment R^5 represents hydrogen.

Representative examples of R^5 include hydrogen.

In a preferred embodiment R^6 represents hydrogen.

In a more preferred embodiment R^6 is methyl.

Representative examples of R^6 include hydrogen and methyl.

In a preferred embodiment there exists a subgroup of formula (1A) wherein
R^1 is 2,3-dihydro-1-benzofuran-4-yl or 4-fluoro-3-(methyloxy)phenyl;

R^2 is hydrogen;

R^3 is selected from:

C_{1-4} alkyl optionally substituted by methoxy or methylsulphonyl;

Pyridyl$(CH_2)_m$-;

Methylpyrazolyl;

Tetrahydropyranyl;

R^4 is hydrogen or methyl;

R^5 is hydrogen;

R^6 is methyl.

In a preferred embodiment there exists a subgroup of formula (1B) wherein R^1 is 2,3-dihydro-1-benzofuran-4-yl, 1-methyl-1H-indazol-6-yl or 4-fluoro-3-(methyloxy)phenyl;

R^2 is hydrogen;

In a preferred embodiment R^3 and R^4 together with the nitrogen atom to which they are attached form a morpholinyl, a 2,6-dimethyl-4-morpholinyl, a 3-(ethoxycarbonyl)-1-piperidinyl, a 4-(*N,N*-dimethylamino)1-piperidinyl, a 4-acetyl-1-piperazinyl or a 4-[(2-methyloxy)ethyl]-1-piperazinyl ring.

R^5 is hydrogen;

R^6 is methyl.

It is to be understood that the present invention covers all combinations of substituent groups referred to hereinabove.

It is to be understood that the present invention covers all combinations of particular and preferred groups described hereinabove.

Particular compounds according to the invention include those mentioned in the examples and their pharmaceutically acceptable salts. Specific examples which may be mentioned include:
Example 1: 4-{[3-(methyloxy)phenyl]amino}-*N*^{6}-phenyl-3,6-quinolinedicarboxamide,
Example 2: 4-{[3-(methyloxy)phenyl]amino}-6-(4-morpholinylcarbonyl)-3-quinolinecarboxamide,
Example 7: *N*^{6},*N*^{6}-dimethyl-4-{[3-(methyloxy)phenyl]amino}-3,6-quinolinedicarboxamide,
Example 8: *N*^{6}-1,3-benzothiazol-6-yl-4-{[3-(methyloxy)phenyl]amino}-3,6-quinolinedicarboxamide,
Example 10: *N*^{6}-(1-methyl-1*H*-benzimidazol-5-yl)-4-{[3-(methyloxy)phenyl]amino}-3,6-quinolinedicarboxamide,
Example 13: 4-{[3-(methyloxy)phenyl]amino}-*N*^{6}-3-pyridinyl-3,6-quinolinedicarboxamide,

Example 14: N^6-[3-(methyloxy)phenyl]-4-{[3-(methyloxy)phenyl]amino}-3,6-quinolinedicarboxamide,
Example 16: N^6-1,3-benzodioxol-5-yl-4-{[3-(methyloxy)phenyl]amino}-3,6-quinolinedicarboxamide,
Example 17: 4-{[3-(methyloxy)phenyl]amino}-N^6-(3-oxo-2,3-dihydro-1*H*-inden-5-yl)-3,6-quinolinedicarboxamide,
Example 22: 4-{[3-(methyloxy)phenyl]amino}-N^6-[6-(methyloxy)-3-pyridinyl]-3,6-quinolinedicarboxamide,
Example 26: N^6-(4-chlorophenyl)-4-{[3-(methyloxy)phenyl]amino}-3,6-quinolinedicarboxamide,
Example 27: 4-{[3-(methyloxy)phenyl]amino}-6-(1-piperidinylcarbonyl)-3-quinolinecarboxamide,
Example 30: 4-{[3-(methyloxy)phenyl]amino}-N^6-(1,3-thiazol-2-ylmethyl)-3,6-quinolinedicarboxamide,
Example 31: N^6-(1,3-dihydro-2-benzofuran-5-yl)-4-{[3-(methyloxy)phenyl]amino}-3,6-quinolinedicarboxamide,
Example 32: N^6-[(3-methyl-5-isoxazolyl)methyl]-4-{[3-(methyloxy)phenyl]amino}-3,6-quinolinedicarboxamide,
Example 33: N^6-[(5-chloro-2-pyridinyl)methyl]-4-{[3-(methyloxy)phenyl]amino}-3,6-quinolinedicarboxamide,
and pharmaceutically acceptable salts thereof.

Further specific examples which may be mentioned include:
Example 34: 4-(2,3-dihydro-1-benzofuran-4-ylamino)-8-methyl-6-(4-morpholinylcarbonyl)-3-quinolinecarboxamide,
Example 38: 8-methyl-4-[(1-methyl-1H-indazol-6-yl)amino]-6-(4-morpholinylcarbonyl)-3-quinolinecarboxamide,
Example 39: 4-{[4-fluoro-3-(methyloxy)phenyl]amino}-8-methyl-6-(4-morpholinylcarbonyl)-3-quinolinecarboxamide,
Example 47: 4-{[4-fluoro-3-(methyloxy)phenyl]amino}-N~6~,8-dimethyl-N~6~-[2-(methyloxy)ethyl]-3,6-quinolinedicarboxamide,
Example 49: 4-{[4-fluoro-3-(methyloxy)phenyl]amino}-N~6~,8-dimethyl-N~6~-[2-(methylsulfonyl)ethyl]-3,6-quinolinedicarboxamide,
Example 55: 6-[(4-acetyl-1-piperazinyl)carbonyl]-4-{[4-fluoro-3-(methyloxy)phenyl]amino}-8-methyl-3-quinolinecarboxamide,
Example 61: 4-(2,3-dihydro-1-benzofuran-4-ylamino)-N~6~,8-dimethyl-N~6~-[2-(methyloxy)ethyl]-3,6-quinolinedicarboxamide,
Example 62: 4-(2,3-dihydro-1-benzofuran-4-ylamino)-N~6~,N~6~,8-trimethyl-3,6-quinolinedicarboxamide,
Example 64: 4-(2,3-dihydro-1-benzofuran-4-ylamino)-8-methyl-6-({4-[2-(methyloxy)ethyl]-1-piperazinyl}carbonyl)-3-quinolinecarboxamide,

Example 65: 4-(2,3-dihydro-1-benzofuran-4-ylamino)-6-[(2,6-dimethyl-4-morpholinyl)carbonyl]-8-methyl-3-quinolinecarboxamide,
Example 66: 4-(2,3-dihydro-1-benzofuran-4-ylamino)-6-{[4-(dimethylamino)-1-piperidinyl]carbonyl}-8-methyl-3-quinolinecarboxamide,
Example 68: 4-(2,3-dihydro-1-benzofuran-4-ylamino)-N~6~,8-dimethyl-N~6~-(4-pyridinylmethyl)-3,6-quinolinedicarboxamide,
Example 70: 6-[(4-acetyl-1-piperazinyl)carbonyl]-4-(2,3-dihydro-1-benzofuran-4-ylamino)-8-methyl-3-quinolinecarboxamide,
Example 72: 4-(2,3-dihydro-1-benzofuran-4-ylamino)-8-methyl-N~6~-4-pyridinyl-3,6-quinolinedicarboxamide,
Example 73: 4-(2,3-dihydro-1-benzofuran-4-ylamino)-8-methyl-N~6~-(tetrahydro-2H-pyran-4-yl)-3,6-quinolinedicarboxamide,
Example 74: 4-(2,3-dihydro-1-benzofuran-4-ylamino)-8-methyl-N~6~-(1-methyl-1H-pyrazol-5-yl)-3,6-quinolinedicarboxamide.

Salts of the compounds of the present invention are also encompassed within the scope of the invention. Because of their potential use in medicine, the salts of the compounds of formula (I) are preferably pharmaceutically acceptable. Suitable pharmaceutically acceptable salts can include acid or base addition salts. A pharmaceutically acceptable acid addition salt can be formed by reaction of a compound of formula (I) with a suitable inorganic or organic acid (such as hydrobromic, hydrochloric, sulfuric, nitric, phosphoric, succinic, maleic, acetic, fumaric, citric, tartaric, benzoic, *p*-toluenesulfonic, methanesulfonic or naphthalenesulfonic acid), optionally in a suitable solvent such as an organic solvent, to give the salt which is usually isolated for example by crystallisation and filtration. A pharmaceutically acceptable acid addition salt of a compound of formula (I) can be for example a hydrobromide, hydrochloride, sulfate, nitrate, phosphate, succinate, maleate, acetate, fumarate, citrate, tartrate, benzoate, *p*-toluenesulfonate, methanesulfonate or naphthalenesulfonate salt. A pharmaceutically acceptable base addition salt can be formed by reaction of a compound of formula (I) with a suitable inorganic or organic base, optionally in a suitable solvent such as an organic solvent, to give the base addition salt which is usually isolated for example by crystallisation and filtration. Other non-pharmaceutically acceptable salts, eg. oxalates or trifluoroacetates, may be used, for example in the isolation of compounds of the invention, and are included within the scope of this invention. The invention includes within its scope all possible stoichiometric and non-stoichiometric forms of the salts of the compounds of formula (I). Also included within the scope of the invention are all solvates, hydrates and complexes of compounds and salts of the invention.

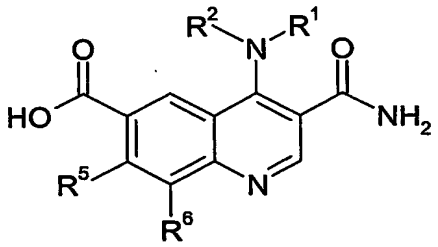
Certain compounds of formula (I) may exist in stereoisomeric forms (e.g. they may contain one or more asymmetric carbon atoms or may exhibit *cis-trans* isomerism). The

individual stereoisomers (enantiomers and diastereomers) and mixtures of these are included within the scope of the present invention. The present invention also covers the individual isomers of the compounds represented by formula (I) as mixtures with isomers thereof in which one or more chiral centres are inverted. Likewise, it is understood that compounds of formula (I) may exist in tautomeric forms other than that shown in the formula and these are also included within the scope of the present invention.

The compounds of this invention may be made by a variety of methods, including standard chemistry. Any previously defined variable will continue to have the previously defined meaning unless otherwise indicated. Illustrative general synthetic methods are set out below and then specific compounds of the invention are prepared in the working Examples.

Process a

Compounds of formula (I), wherein R^1, R^2, R^3, R^4, R^5 and R^6 are as defined above, may be prepared from compounds of formula (II);

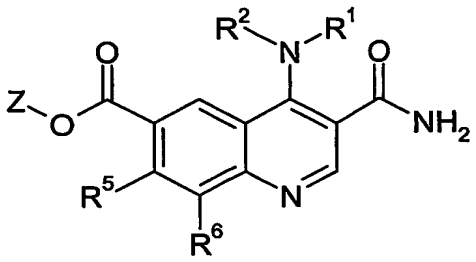


(II)

wherein R^1, R^2, R^5 and R^6 are as defined above, by treatment with a suitable amide coupling agent followed by treatment with an amine of formula R^3R^4NH wherein R^3 and R^4 are as defined above.

Suitable conditions for process a) include stirring in a suitable solvent such as *N,N*-dimethylformamide, at a suitable temperature, such as room temperature in the presence of a suitable coupling reagent such as 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate, optionally in the presence of a suitable base, such as *N,N*-diisopropylethylamine, for a suitable period of time, such as 30 minutes followed by the addition of the amine of formula R^3R^4NH, wherein R^3 and R^4 are as defined above.

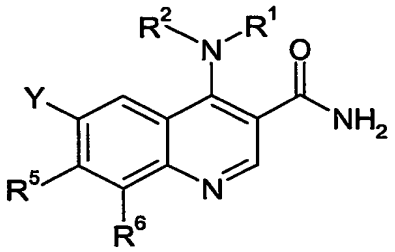
Compounds of formula (II), wherein R^1, R^2, R^5 and R^6 are as defined above, may be prepared from compounds of formula (III);



(III)

wherein R^1, R^2, R^5 and R^6 are as defined above and Z represents C_{1-6} alkyl, by hydrolysis with a suitable base, such as aqueous sodium hydroxide, in a suitable solvent, such as ethanol, at a suitable temperature, such as between room temperature and the reflux temperature of the solvent, for example at room temperature. Alternatively compounds of formula (II) may be prepared from compounds of formula (III) by hydrolysis with a suitable alternative base, such as lithium hydroxide, in a suitable solvent, such as aqueous tetrahydrofuran, at a suitable temperature, such as between room temperature and the reflux temperature of the solvent, for example at 60°C.

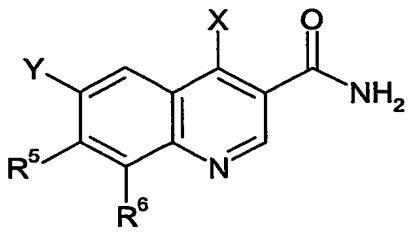
Compounds of formula (III), wherein R^1, R^2, R^5, R^6 and Z are as defined above, may be prepared from compounds of formula (IV);



(IV)

wherein R^1, R^2, R^5 and R^6 are as defined above, and Y represents chlorine, bromine or iodine, by treatment with carbon monoxide and a suitable alcohol such as ethanol in a suitable solvent such as ethanol, at a suitable temperature such as the reflux temperature of the solvent, in the presence of a suitable catalyst, such as a palladium catalyst, *e.g.* dichlorobis(triphenylphosphine)palladium(II) and a suitable base, such as triethylamine.

Compounds of formula (IV), wherein R^1, R^2, R^5, R^6 and Y are as defined above, may be prepared from compounds of formula (V);

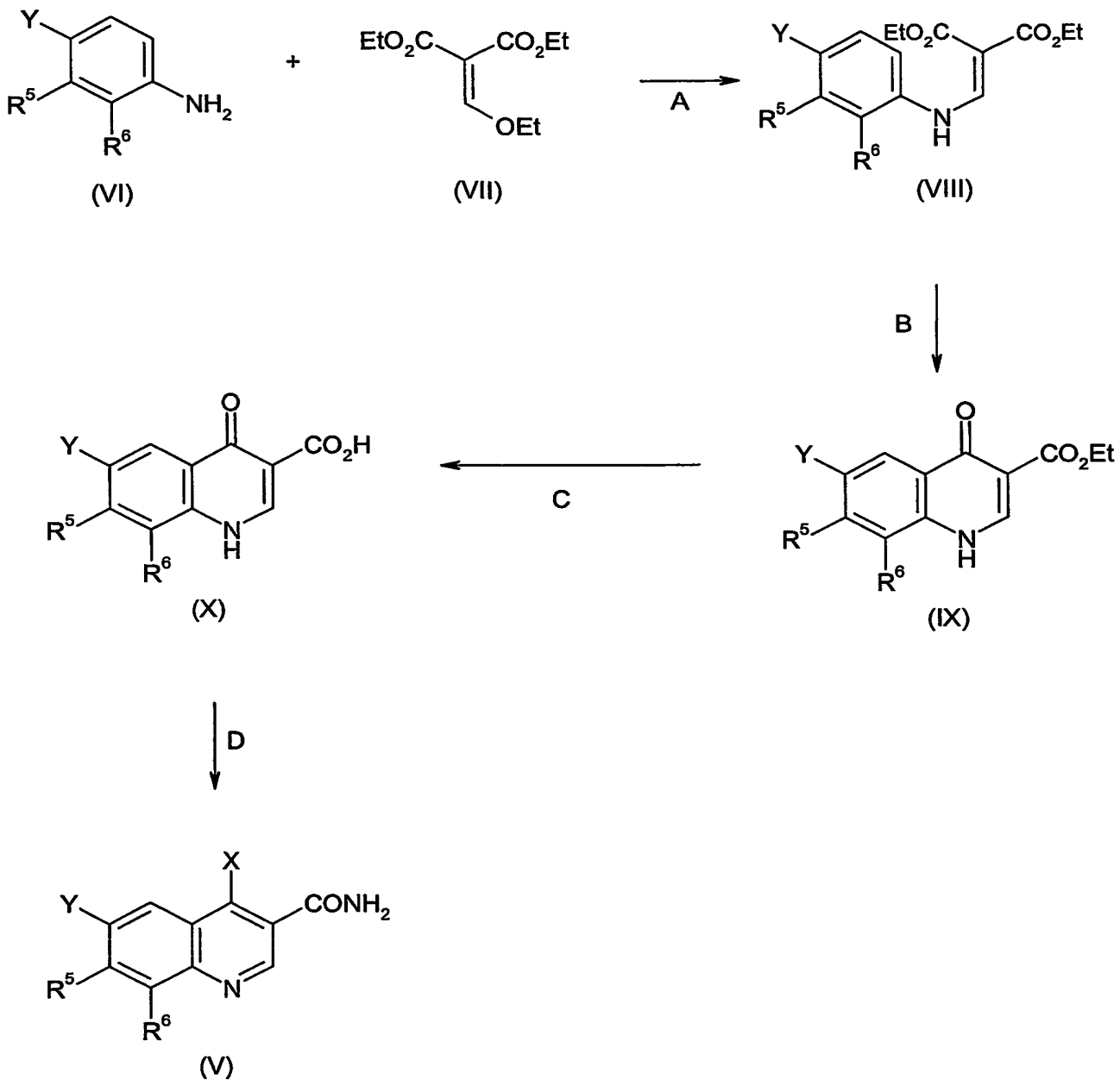


(V)

wherein R^5, R^6 and Y are as defined above and X represents a halogen, by treatment with an amine of formula R^1R^2NH, wherein R^1 and R^2 are as defined above. Suitable conditions include stirring in a suitable solvent such as acetonitrile, at a suitable temperature, such as between room temperature and the reflux temperature of the solvent, for example at 80°C, optionally in the presence of a base such as *N,N*-diisopropylethylamine, or in the presence of an acid catalyst such as pyridine hydrochloride. Alternatively, preparation of compounds of formula (IV) from compounds of formula (V) may be carried out under microwave irradiation, at a suitable power such as 150W, in a suitable solvent such as *N*-methyl-2-pyrrolidinone, at a suitable temperature such as 150°C.

The compounds of formula (V) may be prepared according to the following synthetic scheme, wherein R^5, R^6, X and Y are as defined above:

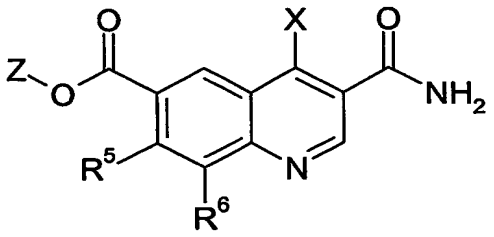
SCHEME 1



Suitable conditions for the reactions of Scheme 1 are: (A) heating together compounds of formulae (VI) and (VII) in the absence of solvent, at a suitable temperature, such as 60-150°C, for example at 100°C; (B) heating compounds of formula (VIII) in a suitable

solvent, such as diphenyl ether, at a suitable temperature such as 200-300°C, for example at 250°C; (C) hydrolysis of compounds of formula (IX) with a suitable base, such as aqueous sodium hydroxide, in a suitable solvent, such as ethanol, at a suitable temperature such as room temperature; (D) treatment of compounds of formula (X) with a suitable halogenating agent, such as a chlorinating agent, for example thionyl chloride, in the presence of a suitable catalyst such as *N,N*-dimethylformamide, followed by treatment with ammonia under suitable conditions, such as concentrated aqueous ammonia at room temperature.

Compounds of formula (III), wherein R^1, R^2, R^5, R^6 and Z are as defined above, may alternatively be prepared from compounds of formula (XIII), wherein R^5, R^6, Z and X are as defined above, by treatment with an amine of formula R^1R^2NH, wherein R^1 and R^2 are as defined above. Suitable conditions include stirring in a suitable solvent such as acetonitrile, at a suitable temperature, such as between room temperature and the reflux temperature of the solvent, for example at 80°C, optionally in the presence of a base such as *N,N*-diisopropylethylamine, or in the presence of an acid catalyst such as pyridine hydrochloride.



(XIII)

Preparation of the compounds of formulae (VIII) and (IX) wherein Y represents iodine and R^5 and R^6 both represent hydrogen have been previously described in: Indian Journal of Chemistry, Section B: Organic Chemistry Including Medicinal Chemistry (2002), 41B(3), 650-652. Preparation of the compound of formula (X) wherein Y represents iodine and R^5 and R^6 both represent hydrogen has been previously described in: PCT Int. Appl. (1999), WO 9932450 A1.

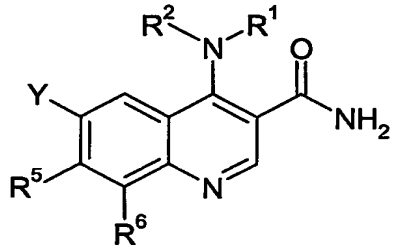
Compounds of formulae (VI) and (VII) are either known compounds (for example available from commercial suppliers such as Aldrich) or may be prepared by conventional means.

Compounds of formulae R^1R^2NH and R^3R^4NH , wherein R^1, R^2, R^3 and R^4 are as defined above, are either known compounds (for example available from commercial suppliers such as Aldrich) or may be prepared by conventional means.

Compounds of formulae R^1R^2NH and R^3R^4NH may contain amine or acid groups which are suitably protected. Examples of suitable protecting groups and the means for their removal can be found in T. W. Greene and P. G. M. Wuts 'Protective Groups in Organic Synthesis' (3rd Ed., J. Wiley and Sons, 1999). Removal of such protecting groups may be accomplished at any suitable stage in the synthesis of compounds of formula (I).

Process b

Compounds of formula (I), wherein R^1, R^2, R^3, R^4, R^5 and R^6 are as defined above, may alternatively be prepared from compounds of formula (IV);



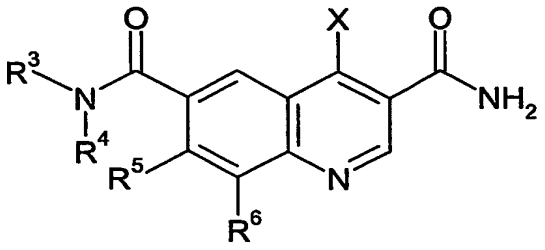
(IV)

wherein R^1, R^2, R^5 and R^6 and Y are as defined above.

Suitable conditions for process b) include treatment with carbon monoxide and an amine of formula R^3R^4NH, wherein R^3 and R^4 are as defined above, in a suitable solvent such as toluene, at a suitable temperature such as the reflux temperature of the solvent, in the presence of a suitable catalyst, such as a palladium catalyst, *e.g.* dichlorobis(triphenylphosphine)palladium(II) and a suitable base, such as triethylamine.

Process c

Compounds of formula (I), wherein R^1, R^2, R^3, R^4, R^5 and R^6 are as defined above, may alternatively be prepared from compounds of formula (XI);

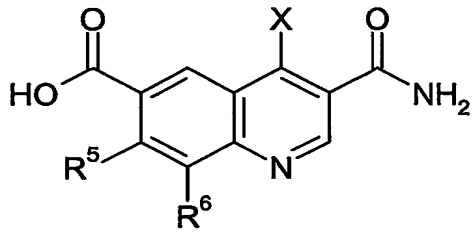


(XI)

wherein R^3, R^4, R^5, R^6 and X are as defined above, by treatment with an amine of formula R^1R^2NH, wherein R^1 and R^2 are as defined above.

Suitable conditions for process c) include stirring in a suitable solvent such as acetonitrile, at a suitable temperature, such as between room temperature and the reflux temperature of the solvent, for example at 80°C, optionally in the presence of a base such as *N,N*-diisopropylethylamine. Alternatively, preparation of compounds of formula (I) from compounds of formula (XI) may be carried out under microwave irradiation, at a suitable power such as 150W, in a suitable solvent such as *N*-methyl-2-pyrrolidinone, at a suitable temperature such as 150°C.

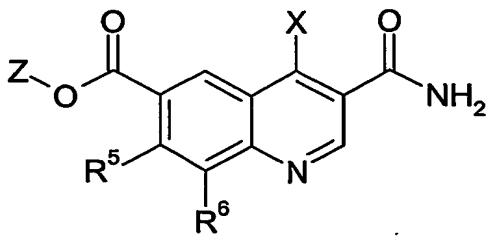
Compounds of formula (XI), wherein R^3, R^4, R^5, R^6 and X are as defined above, may be prepared from compounds of formula (XII);



(XII)

wherein R^5, R^6 and X are as defined above, by treatment with a suitable amide coupling agent followed by treatment with an amine of formula R^3R^4NH wherein R^3 and R^4 are as defined above. Suitable conditions include stirring in a suitable solvent such as *N,N*-dimethylformamide, at a suitable temperature, such as room temperature in the presence of a suitable coupling reagent such as 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate, optionally in the presence of a suitable base, such as *N,N*-diisopropylethylamine, for a suitable period of time, such as 30 minutes followed by the addition of the amine of formula R^3R^4NH, wherein R^3 and R^4 are as defined above.

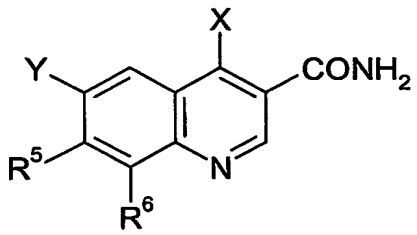
Compounds of formula (XII), wherein R^5, R^6 and X are as defined above, may be prepared from compounds of formula (XIII);



(XIII)

wherein R^5, R^6, Z and X are as defined above, by hydrolysis with a suitable base, such as aqueous sodium hydroxide, in a suitable solvent, such as ethanol, at a suitable temperature, such as between room temperature and the reflux temperature of the solvent, for example at room temperature.

Compounds of formula (XIII), wherein R^5, R^6, Z and X are as defined above, may be prepared from compounds of formula (V);



(V)

wherein R^5, R^6, X and Y are as defined above, by treatment with carbon monoxide and a suitable alcohol such as ethanol, in a suitable solvent such as ethanol, at a suitable temperature such as the reflux temperature of the solvent, in the presence of a suitable catalyst, such as a palladium catalyst, *e.g.* dichlorobis(triphenylphosphine)palladium(II) or palladium acetate, and a suitable base, such as triethylamine.

Process d

Compounds of formula (I) may also be prepared by a process of interconversion between compounds of formula (I). Processes of interconversion between compounds of formula (I) may include, for example oxidation, reduction, alkylation, dealkylation, or substitution.

Process e

Compounds of formula (I) may also be prepared by a process of deprotection of protected derivatives of compounds of formula (I). Examples of suitable protecting groups and the means for their removal can be found in T. W. Greene 'Protective Groups in Organic Synthesis' (J. Wiley and Sons, 1991).

The present invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use as an active therapeutic substance in a mammal such as a human. The compound or salt can be for use in the treatment and/or prophylaxis of any of the conditions described herein and/or for use as a phosphodiesterase inhibitor, *e.g.* for use as a phosphodiesterase 4 (PDE4) inhibitor. "Therapy" may include treatment and/or prophylaxis.

Also provided is the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament (*e.g.* pharmaceutical composition) for the treatment and/or prophylaxis of an inflammatory and/or allergic disease in a mammal such as a human.

Also provided is a method of treatment and/or prophylaxis of an inflammatory and/or allergic disease in a mammal (*e.g.* human) in need thereof, which comprises administering to the mammal (*e.g.* human) a therapeutically effective amount of a compound of formula (I) as herein defined or a pharmaceutically acceptable salt thereof.

Phosphodiesterase 4 inhibitors are believed to be useful in the treatment and/or prophylaxis of a variety of diseases, especially inflammatory and/or allergic diseases, in mammals such as humans, for example: asthma, chronic bronchitis, emphysema, atopic dermatitis, urticaria, allergic rhinitis (seasonal or perennial), vasomotor rhinitis, nasal polyps, allergic conjunctivitis, vernal conjunctivitis, occupational conjunctivitis, infective conjunctivitis, eosinophilic syndromes, eosinophilic granuloma, psoriasis, rheumatoid arthritis, chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema, septic shock, ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium and brain, chronic glomerulonephritis, endotoxic shock, adult respiratory distress syndrome, multiple sclerosis, or memory impairment (including Alzheimer's disease) pain or depression.

In the treatment and/or prophylaxis, the inflammatory and/or allergic disease is preferably chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema, asthma, rheumatoid arthritis, or allergic rhinitis, atopic dermatitis or psoriasis in a mammal (*e.g.* human). More preferably, the treatment and/or prophylaxis is

of COPD including chronic bronchitis and emphysema, or asthma or allergic rhinitis in a mammal (*e.g.* human). PDE4 inhibitors are thought to be effective in the treatment of asthma (*e.g.* see M.A.Giembycz, *Drugs*, Feb. 2000, **59(2)**, 193-212; Z. Huang et al., *Current Opinion in Chemical Biology*, 2001, **5**, 432-438; and refs cited therein) and COPD (*e.g.* see S.L. Wolda, *Emerging Drugs*, 2000, **5(3)**, 309-319; Z. Huang et al., *Current Opinion in Chemical Biology*, 2001, **5**, 432-438; and refs cited therein). COPD is often characterised by the presence of airflow obstruction due to chronic bronchitis and/or emphysema (S.L. Wolda, *Emerging Drugs*, 2000, **5(3)**, 309-319).

PDE4 inhibitors are thought to be effective in the treatment of allergic rhinitis (e.g. see B.M. Schmidt et al., *J. Allergy & Clinical Immunology*, 108(4), 2001, 530-536).

PDE4 inhibitors are thought to be effective in the treatment of rheumatoid arthritis and multiple sclerosis (e.g. see H.J.Dyke et al., *Expert Opinion on Investigational Drugs*, January 2002, 11(1), 1-13; C.Burnouf et al., *Current Pharmaceutical Design*, 2002, 8(14), 1255-1296; and A.M.Doherty, *Current Opinion Chem. Biol.*, 1999, 3(4), 466-473; and refs cited therein). See e.g. A.M.Doherty, *Current Opinion Chem. Biol.*, 1999, 3(4), 466-473 and refs cited therein for atopic dermatitis use.

PDE4 inhibitors have been suggested as having analgesic properties and thus being effective in the treatment of pain (A.Kumar et al., *Indian J. Exp. Biol.*, 2000, 38(1), 26-30).

In the invention, the treatment and/or prophylaxis can be of cognitive impairment e.g. cognitive impairment in a neurological disorder such as Alzheimer's disease. For example, the treatment and/or prophylaxis can comprise cognitive enhancement e.g. in a neurological disorder. See for example: H.T.Zhang et al. in: *Psychopharmacology*, June 2000, 150(3), 311-316 and *Neuropsychopharmacology*, 2000, 23(2), 198-204; and T. Egawa et al., *Japanese J. Pharmacol.*, 1997, 75(3), 275-81.

PDE4 inhibitors such as rolipram have been suggested as having antidepressant properties (e.g. J. Zhu et al., *CNS Drug Reviews*, 2001, 7(4), 387-398; O'Donnell, *Expert Opinion on Investigational Drugs*, 2000, 9(3), 621-625; and H.T. Zhang et al., *Neuropsychopharmacology*, October 2002, 27(4), 587-595).

For use in medicine, the compounds of the present invention are usually administered as a pharmaceutical composition.

The present invention therefore provides in a further aspect a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable carriers and/or excipients.

The pharmaceutical composition can be for use in the treatment and/or prophylaxis of any of the conditions described herein.

The compounds of formula (I) and/or the pharmaceutical composition may be administered, for example, by oral, parenteral (*e.g.* intravenous, subcutaneous, or intramuscular), inhaled, nasal, transdermal or rectal administration, or as topical treatments (*e.g.* lotions, solutions, creams, ointments or gels). Accordingly, the pharmaceutical composition is preferably suitable for oral, parenteral (*e.g.* intravenous, subcutaneous or intramuscular), topical, inhaled or nasal administration. More preferably, the pharmaceutical composition is suitable for topical, inhaled or oral administration, *e.g.* to a mammal such as a human. Inhaled administration involves topical administration to the lung, *e.g.* by aerosol or dry powder composition.

A pharmaceutical composition suitable for oral administration can be liquid or solid; for example it can be a solution, a syrup, a suspension or emulsion, a tablet, a capsule or a lozenge.

A liquid formulation will generally consist of a suspension or solution of the compound or pharmaceutically acceptable salt in a suitable pharmaceutically acceptable liquid carrier(s), for example an aqueous solvent such as water, aqueous ethanol or aqueous glycerine, or an oil, or a non-aqueous solvent, such as a surfactant, such as polyethylene glycol or an oil. The formulation may also contain a suspending agent, preservative, flavouring and/or colouring agent.

A pharmaceutical composition suitable for oral administration being a tablet can comprise one or more pharmaceutically acceptable carriers and/or excipients suitable for preparing tablet formulations. Examples of such carriers include lactose and cellulose. The tablet can also or instead contain one or more pharmaceutically acceptable excipients, for example binding agents, lubricants such as magnesium stearate, and/or tablet disintegrants.

A pharmaceutical composition suitable for oral administration being a capsule can be prepared using encapsulation procedures. For example, pellets containing the active ingredient can be prepared using a suitable pharmaceutically acceptable carrier and then filled into a hard gelatin capsule. Alternatively, a dispersion, or suspension or solution can be prepared using any suitable pharmaceutically acceptable carrier, for example an aqueous solution, aqueous gum or an oil and the dispersion, or suspension or solution then filled into a soft or hard gelatin capsule.

The compounds of formula (I) and/or the pharmaceutical composition may be administered by a controlled or sustained release formulation as described in WO 00/50011.

A parenteral composition can comprise a solution or suspension of the compound or pharmaceutically acceptable salt in a sterile aqueous carrier or parenterally acceptable oil. Alternatively, the solution can be lyophilised; the lyophilised parenteral pharmaceutical composition can be reconstituted with a suitable solvent just prior to administration.

Compositions for nasal or inhaled administration may conveniently be formulated as aerosols, solutions, drops, gels or dry powders.

For compositions suitable and/or adapted for inhaled administration, it is preferred that the compound or salt of formula (I) is in a particle-size-reduced form, and more preferably the size-reduced form is obtained or obtainable by micronisation. The preferable particle size of the size-reduced (e.g. micronised) compound or salt is defined by a D50 value of about 0.5 to about 10 microns (for example as measured using laser diffraction).

Aerosol formulations, *e.g.* for inhaled administration, can comprise a solution or fine suspension of the active substance in a pharmaceutically acceptable aqueous or non-aqueous solvent. Aerosol formulations can be presented in single or multidose quantities in sterile form in a sealed container, which can take the form of a cartridge or refill for use with an atomising device or inhaler. Alternatively the sealed container may be a unitary dispensing device such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve (metered dose inhaler) which is intended for disposal once the contents of the container have been exhausted.

Where the dosage form comprises an aerosol dispenser, it preferably contains a suitable propellant under pressure such as compressed air, carbon dioxide or an organic propellant such as a hydrofluorocarbon (HFC). Suitable HFC propellants include 1,1,1,2,3,3,3-heptafluoropropane and 1,1,1,2-tetrafluoroethane. The aerosol dosage forms can also take the form of a pump-atomiser. The pressurised aerosol may contain a solution or a suspension of the active compound. This may require the incorporation of additional excipients e.g. co-solvents and/or surfactants to improve the dispersion characteristics and homogeneity of suspension formulations. Solution formulations may also require the addition of co-solvents such as ethanol. Other excipient modifiers may also be incorporated to improve, for example, the stability and/or taste and/or fine particle mass characteristics (amount and/or profile) of the formulation.

For pharmaceutical compositions suitable and/or adapted for inhaled administration, it is preferred that the pharmaceutical composition is a dry powder inhalable composition. Such a composition can comprise a powder base such as lactose, glucose, trehalose, mannitol or starch, the compound of formula (I) or salt thereof (preferably in particle-size-reduced form, e.g. in micronised form), and optionally a performance modifier such as L-leucine or another amino acid, cellobiose octaacetate and/or metals salts of stearic acid such as magnesium or calcium stearate. Preferably, the dry powder inhalable composition comprises a dry powder blend of lactose and the compound of formula (I) or salt thereof. The lactose is preferably lactose hydrate e.g. lactose monohydrate and/or is preferably inhalation-grade and/or fine-grade lactose. Preferably, the particle size of the lactose is defined by 90% or more (by weight or by volume) of the lactose particles being less than 1000 microns (micrometres) (e.g. 10-1000 microns e.g. 30-1000 microns) in diameter, and/or 50% or more of the lactose particles being less than 500 microns (e.g. 10-500 microns) in diameter. More preferably, the particle size of the lactose is defined by 90% or more of the lactose particles being less than 300 microns (e.g. 10-300 microns e.g. 50-300 microns) in diameter, and/or 50% or more of the lactose particles being less than 100 microns in diameter. Optionally, the particle size of the lactose is defined by 90% or more of the lactose particles being less than 100-200 microns in diameter, and/or 50% or more of the lactose particles being less than 40-70 microns in diameter. Most importantly, it is preferable that about 3 to about 30% (e.g. about 10%) (by weight or by volume) of the particles are less than 50 microns or less than 20 microns in diameter. For example, without limitation, a suitable inhalation-grade lactose is E9334 lactose (10% fines) (Borculo Domo Ingredients, Hanzeplein 25, 8017 JD Zwolle, Netherlands).

Optionally, in particular for dry powder inhalable compositions, a pharmaceutical composition for inhaled administration can be incorporated into a plurality of sealed dose containers (*e.g.* containing the dry powder composition) mounted longitudinally in a strip or ribbon inside a suitable inhalation device. The container is rupturable or peel-openable on demand and the dose of *e.g.* the dry powder composition can be administered by inhalation via the device such as the DISKUS ^{TM} device, marketed by GlaxoSmithKline. The DISKUS ^{TM} inhalation device is for example described in GB 2242134 A, and in such a device at least one container for the pharmaceutical composition in powder form (the container or containers preferably being a plurality of sealed dose containers mounted longitudinally in a strip or ribbon) is defined between two members peelably secured to one another; the device comprises: a means of defining an opening station for the said container or containers; a means for peeling the members apart at the opening station to open the container; and an outlet, communicating with the opened container, through which a user can inhale the pharmaceutical composition in powder form from the opened container.

For application topically to the skin, the compound of formula (I) or a pharmaceutically acceptable salt thereof could be formulated as a suitable ointment containing the active compound suspended or dissolved in, for example, a mixture with one or more of the following: mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water. Alternatively, it could be formulated as a suitable lotion or cream, suspended or dissolved in, for example, a mixture of one or more of the following: mineral oil, sorbitan monostearate, a polyethylene glycol, liquid paraffin, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

In the pharmaceutical composition, each dosage unit for oral or parenteral administration preferably contains from 0.01 to 3000 mg, more preferably 0.5 to 1000 mg, of a compound of the formula (I) or a pharmaceutically acceptable salt thereof, calculated as the free base. Each dosage unit for nasal or inhaled administration preferably contains from 0.001 to 50 mg, more preferably 0.005 to 5 mg, of a compound of the formula (I) or a pharmaceutically acceptable salt thereof, calculated as the free base.

The pharmaceutically acceptable compounds or salts of the invention can be administered in a daily dose (for an adult patient) of, for example, an oral or parenteral dose of 0.01 mg to 3000 mg per day or 0.5 to 1000 mg per day, or a nasal or inhaled dose of 0.001 to 50 mg per day or 0.005 to 5 mg per day, of the compound of the formula (I) or a pharmaceutically acceptable salt thereof, calculated as the free base.

The compounds, salts and/or pharmaceutical compositions according to the invention may also be used in combination with one or more other therapeutically active agents, for example, a β_2 adrenoreceptor agonist, an anti-histamine, an anti-allergic agent, an anti-inflammatory agent (including a steroid), an anticholinergic agent or an antiinfective agent (*e.g.* antibiotics or antivirals).

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof with one or more other therapeutically active agents, for example, a β_2-adrenoreceptor agonist, an anti-histamine, an anti-allergic agent, an anti-inflammatory agent (including a steroid), an anticholinergic agent or an antiinfective agent (*e.g.* antibiotics or antivirals).

Examples of β_2-adrenoreceptor agonists include salmeterol (*e.g.* as racemate or a single enantiomer such as the R-enantiomer), salbutamol, formoterol, salmefamol, fenoterol or terbutaline and salts thereof, for example the xinafoate salt of salmeterol, the sulphate salt or free base of salbutamol or the fumarate salt of formoterol. Long-acting β_2-adrenoreceptor agonists are preferred, especially those having a therapeutic effect over a 24 hour period such as salmeterol or formoterol.

Examples of anti-histamines include methapyrilene, or loratadine, cetirizine, desloratadine or fexofenadine.

Examples of anti-inflammatory steroids include fluticasone propionate and budesonide.

Examples of anticholinergic compounds which may be used in combination with a compound of formula (I) or a pharmaceutically acceptable salt thereof are described in WO 03/011274 A2 and WO 02/069945 A2 / US 2002/0193393 A1 and US 2002/052312 A1. For example, anticholinergic agents include muscarinic M3 antagonists, such as ipratropium bromide, oxitropium bromide or tiotropium bromide.

Other suitable combinations include, for example, combinations comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof together with other anti-inflammatory agents (*e.g.* anti-inflammatory corticosteroids, NSAIDs, leukotriene antagonists (e.g. montelukast), iNOS inhibitors, tryptase and elastase inhibitors, beta-2 integrin antagonists, chemokine antagonists such as CCR3 antagonists, and adenosine 2a agonists, 5-lipoxygenase inhibitors and antiinfective agents such as an antibiotic or an antiviral). An iNOS inhibitor is preferably for oral administration. Suitable iNOS inhibitors (inducible nitric oxide synthase inhibitors) include those disclosed in WO 93/13055, WO 98/30537, WO 02/50021, WO 95/34534 and WO 99/62875. Suitable CCR3 inhibitors include those disclosed in WO 02/26722.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical composition and thus a pharmaceutical composition comprising a combination as defined above together with one or more pharmaceutically acceptable carriers and/or excipients represent a further aspect of the invention.

The individual compounds of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical compositions.

Biological Test Methods

PDE3, PDE4B, PDE4D, PDE5 Primary assay methods

The activity of the compounds can be measured as described below. Preferred compounds of the invention are selective PDE4 inhibitors, *i.e.* they inhibit PDE4 (*e.g.* PDE4B and/or PDE4D) more strongly than they inhibit other PDE's such as PDE3 and/or PDE5.

PDE enzyme sources and literature references

Human recombinant PDE4B, in particular the 2B splice variant thereof (HSPDE4B2B), is disclosed in WO 94/20079 and also in M.M. McLaughlin et al., "A low *K*m, rolipram-sensitive, cAMP-specific phosphodiesterase from human brain: cloning and expression of cDNA, biochemical characterisation of recombinant protein, and tissue distribution of mRNA", *J. Biol. Chem.*, 1993, **268**, 6470-6476. For example, in Example 1 of WO 94/20079, human recombinant PDE4B is described as being expressed in the PDE-deficient yeast *Saccharomyces cerevisiae* strain GL62, e.g. after induction by addition of 150 uM $CuSO_4$, and 100,000 x *g* supernatant fractions of yeast cell lysates are described for use in the harvesting of PDE4B enzyme.

Human recombinant PDE4D (HSPDE4D3A) is disclosed in P. A. Baecker et al., "Isolation of a cDNA encoding a human rolipram-sensitive cyclic AMP phoshodiesterase (PDE IV_D)", *Gene*, 1994, **138**, 253-256.

Human recombinant PDE5 is disclosed in K. Loughney et al., "Isolation and characterisation of cDNAs encoding PDE5A, a human cGMP-binding, cGMP-specific 3',5'-cyclic nucleotide phosphodiesterase", *Gene*, 1998, **216**, 139-147.

PDE3 was may be purified from bovine aorta as described by H. Coste and P. Grondin, "Characterisation of a novel potent and specific inhibitor of type V phosphodiesterase", *Biochem. Pharmacol.*, 1995, **50**, 1577-1585.

PDE6 was may be purified from bovine retina as described by: P. Catty and P. Deterre, "Activation and solubilization of the retinal cGMP-specific phosphodiesterase by limited proteolysis", *Eur. J. Biochem.*, 1991, **199**, 263-269; A. Tar et al. "Purification of bovine retinal cGMP phosphodiesterase", *Methods in Enzymology*, 1994, **238**, 3-12; and/or D. Srivastava et al. "Effects of magnesium on cyclic GMP hydrolysis by the bovine retinal rod cyclic GMP phosphodiesterase", *Biochem. J.*, 1995, **308**, 653-658.

Inhibition of PDE3, PDE4B,PDE4D, PDE5 or PDE6 activity: radioactive Scintillation Proximity Assay (SPA)

The ability of compounds to inhibit catalytic activity at PDE4B or 4D (human recombinant), PDE3 (from bovine aorta) PDE5 (human recombinant) or PDE 6 (from bovine retina) was may be determined by Scintillation Proximity Assay (SPA) in 96-well format. Test compounds (preferably as a solution in DMSO, e.g. 2 microlitre (µl) volume) were preincubated at ambient temperature in Wallac Isoplates (code 1450-514) with PDE enzyme in 50mM Tris-HCl buffer pH 7.5 , 8.3mM $MgCl_2$, 1.7mM EGTA, 0.05% (w/v) bovine serum albumin for 10-30 minutes. The enzyme concentration was adjusted so

that control rates are linear over the asay incubation period. For the PDE3, PDE4B and PDE4D assays [5',8-^{3}H]adenosine 3',5'-cyclic phosphate (Amersham Pharmacia Biotech , code TRK.559 or Amersham Biosciences UK Ltd, Pollards Wood, Chalfont St Giles, Buckinghamshire HP8 4SP, UK) was added to give 0.05μCi per well and ~ 10nM final concentration. For the PDE5 and PDE6 assays [8-^{3}H]guanosine 3',5'-cyclic phosphate (Amersham Pharmacia Biotech , code TRK.392) was added to give 0.05μCi per well and ~ 36nM final concentration. Plates e.g. containing approx. 100 μl volume of assay mixture were mixed on an orbital shaker for 5 minutes and incubated at ambient temperature for 1 hour. Phosphodiesterase SPA beads (Amersham Pharmacia Biotech, code RPNQ 0150) were added (~1mg per well) to terminate the assay. Plates were sealed and shaken and allowed to stand at ambient temperature for 35 minutes to 1hour to allow the beads to settle. Bound radioactive product was measured using a WALLAC TRILUX 1450 MicroBeta scintillation counter. For inhibition curves, 10 concentrations (*e.g.* 1.5nM - 30μM) of each compound were assayed; more potent compounds were assayed over lower concentration ranges (assay concentrations were generally between 30μM and 50fM). Curves were analysed using ActivityBase and XLfit (ID Businesss Solutions Limited, 2 Ocean Court, Surrey Research Park, Guildford, Surrey GU2 7QB, United Kindgom). Results were expressed as pIC_{50} values.

Alternatively, the activity of the compounds can be measured in the following Fluorescence Polarisation (FP) assay:

Inhibition of PDE activity: Fluorescence Polarisation (FP) assay

The ability of compounds to inhibit PDE catalytic activity was determined by IMAP Fluorescence Polarisation (FP) assay (Molecular Devices Ltd code: R8062) in 384-well format. Test compounds (small volume, e.g. 0.5 μl, of solution in DMSO) were preincubated at ambient temperature in black 384-well microtitre plates (supplier: NUNC, code 262260) with PDE enzyme in 10mM Tris-HCl buffer pH 7.2, 10mM $MgCl_2$, 0.1% (w/v) bovine serum albumin, 0.05% NaN_3 for 10-30 minutes. The enzyme level was set so that reaction was linear throughout the incubation.

For the PDE3, PDE4B and PDE4D assays Fluorescein adenosine 3',5'-cyclic phosphate (Molecular Devices Ltd code: R7091) was added to give ~ 40nM final concentration. For the PDE5 and PDE6 assays Fluorescein guanosine 3',5'-cyclic phosphate (Molecular Devices Ltd code: R7090) was added to give ~ 40nM final concentration. Plates were mixed on an orbital shaker for 10 seconds and incubated at ambient temperature for 40 minutes. IMAP binding reagent (Molecular Devices Ltd code: R7207) was added (60μl of a 1 in 400 dilution in binding buffer of the kit stock solution) to terminate the assay. Plates were allowed to stand at ambient temperature for 1hour. The FP ratio of parallel to

perpendicular light was measured using an Analyst™ plate reader (from Molecular Devices Ltd). For inhibition curves, 11 concentrations (0.5nM - 30μM) of each compound were assayed; more potent compounds were assayed over lower concentration ranges (assay concentrations were generally between 30μM and 50fM). Curves were analysed using ActivityBase and XLfit (ID Business Solutions Limited). Results were expressed as pIC_{50} values.

For a given PDE4 inhibitor, the PDE4B (or PDE4D) inhibition values measured using the SPA and FP assays can differ slightly. However, in a regression analysis of at least 100 test compounds, the pIC_{50} inhibition values measured using SPA and FP assays have been found generally to agree within 0.5 log units, for PDE4B and PDE4D (linear regression coefficient 0.966 for PDE4B and 0.971 for PDE4D; David R.Mobbs et al., "Comparison of the IMAP Fluorescence Polarisation Assay with the Scintillation Proximity Assay for Phosphodiesterase Activity", poster presented at the 2003 Molecular Devices UK & Europe User Meeting, 2nd October 2003, Down Hall, Harlow, Essex, United Kingdom).

Examples of compounds of the invention described above inhibit the catalytic activity at the PDE4B (human recombinant) enzyme with pIC_{50}'s in the range 6.3-9.5.
Biological Data obtained for some of the Examples PDE4B and PDE5 inhibitory activity) is as follows:

Example No.	PDE4B* mean pIC_{50}	PDE5** mean pIC_{50}
1	8.0	<4.5
2	7.6	<4.5
3	7.4	<4.5
6	6.3	<4.5
60	9.0	4.5

* Examples 1 to 6 tested in SPA assay, Example 60 tested in FP assay
** All Examples tested in SPA assay

Emesis: Many known PDE4 inhibitors cause emesis and/or nausea to greater or lesser extents (*e.g.* see Z. Huang et al., *Current Opinion in Chemical Biology*, 2001, 5, 432-438, see especially pages 433-434 and refs cited therein). Therefore, it would be preferable but not essential that a PDE4 inhibitory compound of the invention causes only limited or manageable emetic side-effects. Emetic side-effects can for example be measured by the emetogenic potential of the compound when administered to ferrets; for

example one can measure the time to onset, extent, frequency and/or duration of vomiting and/or writhing in ferrets after oral or parenteral administration of the compound. See for example A. Robichaud *et al.,* "Emesis induced by inhibitors of PDE IV in the ferret" *Neuropharmacology*, 1999, 38, 289-297, erratum *Neuropharmacology*, 2001, 40, 465-465.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

EXAMPLES

The various aspects of the invention will now be described by reference to the following examples. These examples are merely illustrative and are not to be construed as a limitation of the scope of the present invention. In this section, "Intermediates" represent syntheses of intermediate compounds intended for use in the synthesis of the "Examples".

Abbreviations used herein:

NMR	nuclear magnetic resonance
HPLC	high performance liquid chromatography
LC/MS	liquid chromatography/mass spectroscopy
SPE	solid phase extraction column. Unless otherwise specified the solid phase will be silica gel. Aminopropyl SPE refers to a silica SPE column with aminopropyl residues immobilised on the solid phase (*eg.* IST Isolute™ columns). It is thought that compounds isolated by SPE are free bases.
SCX	solid phase extraction (SPE) column with benzene sulfonic acid residues immobilised on the solid phase (*eg.* IST Isolute™ columns). When eluting with ammonia/ methanol, it is thought that compounds isolated by SCX are free bases.

General experimental details

LC/MS (liquid chromatography/mass spectroscopy)
Waters ZQ mass spectrometer operating in positive ion electrospray mode, mass range 100-1000 amu.
UV wavelength : 215-330nM
Column : 3.3cm x 4.6mm ID, 3μm ABZ+PLUS
Flow Rate : 3ml/min
Injection Volume : 5μl
Solvent A : 95% acetonitrile + 0.05% formic acid
Solvent B : 0.1% formic acid + 10mMolar ammonium acetate
Gradient: Mixtures of Solvent A and Solvent B are used according to the following gradient profiles (expressed as % Solvent A in the mixture): 0% A/0.7min, 0-100% A/3.5min, 100% A/1.1min, 100-0% A/0.2min

Mass Directed Automated Preparative HPLC column, conditions and eluent
Method A

The preparative column used was a Supelcosil ABZplus (10cm x 2.12cm internal diameter; particle size 5μm)
UV detection wavelength : 200-320nM
Flow rate : 20ml/min
Injection Volume: 0.5ml
Solvent A : 0.1% formic acid
Solvent B : 95% acetonitrile + 0.05% formic acid
Gradient systems: mixtures of Solvent A and Solvent B are used according to a choice of 5 generic gradient profiles (expressed as % Solvent B in the mixture), ranging from a start of 0 to 50% Solvent B, with all finishing at 100% Solvent B to ensure total elution.
It is thought that compounds isolated by this method are free bases, unless the R^1 or R^3 groups contain basic moieties, in which case formate salts may be formed.

Mass Directed Automated Preparative HPLC column, conditions and eluent
Method B
The preparative column used was a Supelcosil ABZplus (10cm x 2.12cm internal diameter; particle size 5μm)
UV detection wavelength : 200-320nM
Flow rate : 20ml/min
Injection Volume: 0.5ml
Solvent A : water + 0.1% trifluoroacetic acid
Solvent B : acetonitrile + 0.1% trifluoroacetic acid
Gradient systems: mixtures of Solvent A and Solvent B are used according to a choice of 5 generic gradient profiles (expressed as % Solvent B in the mixture), ranging from a start of 0 to 50% Solvent B, with all finishing at 100% Solvent B to ensure total elution.
It is thought that compounds isolated by this method are trifluoroacetate salts.

Product isolation by filtration directly from the reaction mixture

It is thought that compounds isolated by this method from reactions involving displacement of a 4-chloroquinoline intermediate with an amine of formula R^1R^2NH are hydrochloride salts.

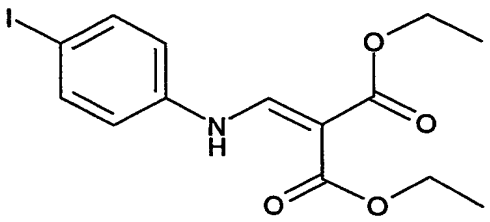
Evaporation of product fractions after purification
Reference to column chromatography, SPE and preparative HPLC purification includes evaporation of the product containing fractions to dryness by an appropriate method.

Aqueous ammonia solutions
'880 Ammonia' or '0.880 ammonia' refers to concentrated aqueous ammonia (specific gravity 0.880).

Intermediates and Examples

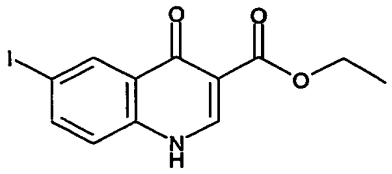
All reagents not detailed in the text below are commercially available from established suppliers such as Sigma-Aldrich.

Intermediate 1. Diethyl {[(4-iodophenyl)amino]methylidene}propanedioate



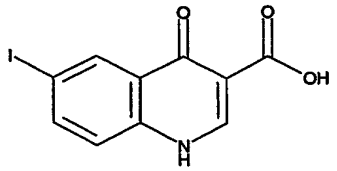
A mixture of 4-iodoaniline (208g) (available from Aldrich) and diethyl (ethoxymethylene)malonate (210ml) (available from Aldrich) was heated to 100°C. The mixture set solid at *ca.* 60°C, and was removed from heating and broken up. Heating was continued at 100°C for 1h, and the solid was collected, washed with cyclohexane (1000ml) and ethanol (2x500ml), and dried *in vacuo* at 40°C overnight to give the title compound as a white solid (356.1g).
LC/MS R_t 3.57min *m/z* 390 [MH^+].

Intermediate 2. Ethyl 6-iodo-4-oxo-1,4-dihydro-3-quinolinecarboxylate



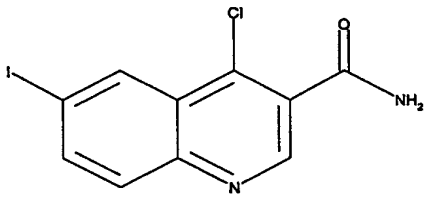
Diphenyl ether (170ml) was heated to reflux and intermediate 1 (30g) was gradually added down an air condenser. Once all the reagent had been added the mixture was heated under reflux for a further 30min. The mixture was then cooled and isohexane (200ml) was added. The solid formed was collected by filtration to give the title compound (19.2g).
NMR(DMSO) δ 8.58 (1H,s), 8.42(1H,d), 7.99 (1H,dd), 7.44(1H,d), 4.21(2H,q), 1.28 (3H,t).

Intermediate 3. 6-Iodo-4-oxo-1,4-dihydro-3-quinolinecarboxylic acid



Sodium hydroxide (9.8g) was dissolved in water (61ml) and ethanol (30ml) was added. The resultant solution was added to intermediate 2, and the mixture was heated under reflux for 60min with stirring under nitrogen. Concentrated hydrochloric acid was added, giving a white precipitate. After stirring for 16h, the precipitate was filtered off, washed with water and dried *in vacuo* to give a white solid (8.15g) as the title compound.
LC/MS R_t 3.01min *m/z* 316 [MH^+].

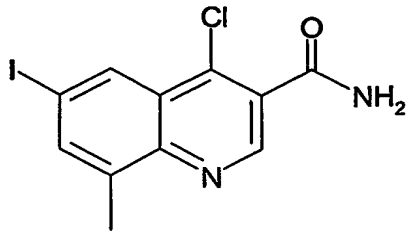
Intermediate 4. 4-Chloro-6-iodo-3-quinolinecarboxamide



Intermediate 3 (8.1g) was added portionwise to stirred thionyl chloride (60ml). *N,N*-dimethylformamide (3 drops) was added and the mixture was heated under reflux with stirring under nitrogen for 1.75h. The excess thionyl chloride was evaporated *in vacuo* and the residue was azeotroped with toluene (2x50ml). The resulting pale yellow solid was added portionwise to stirred concentrated aqueous ammonia (250ml), and the mixture stirred at room temperature for 1.5h. The solid was filtered off, washed with water and dried *in vacuo* at 60°C for 16h to give the title compound as a white solid (7.94g).
LC/MS R_t 2.72min *m/z* 332 [MH^+].

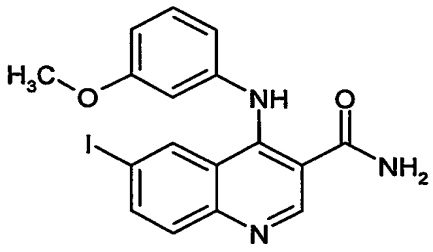
Similarly prepared from 4-iodo-2-methylaniline (available from Aldrich) was

Intermediate 8. 4-Chloro-6-iodo-8-methyl-3-quinolinecarboxamide



LC/MS R_t 3.05min *m/z* 347 [MH^+]

Intermediate 5. 6-Iodo-4-{[3-(methyloxy)phenyl]amino}-3-quinolinecarboxamide hydrochloride

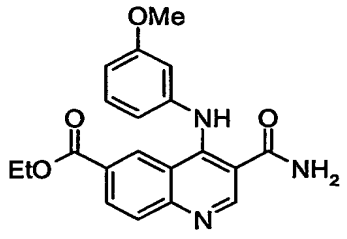


HCl

Intermediate 4 (2.5g) was dissolved in acetonitrile (30ml), 3-methoxyaniline (0.84ml) (available from Aldrich) was added, and the mixture was heated under reflux for 16h. The resulting precipitate was filtered off and washed with acetonitrile to give the title compound (2.2g).

LC/MS R_t 2.53min *m/z* 420 [MH^+]

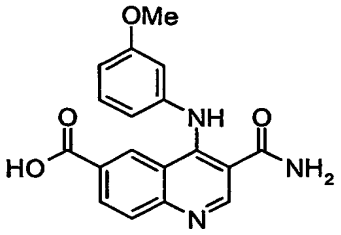
Intermediate 6. Ethyl 3-(aminocarbonyl)-4-{[3-(methyloxy)phenyl]amino}-6-quinolinecarboxylate



To a stirred solution of intermediate 5 (1.0g) in ethanol (50ml) was added triethylamine (0.63ml) and dichlorobis(triphenylphosphine)palladium(II) (0.08g). The flask was evacuated and refilled with nitrogen three times and then evacuated and refilled with carbon monoxide two times. The mixture was heated at 80°C under an atmosphere of

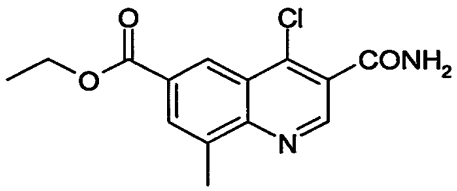
carbon monoxide for 16h. The mixture was cooled to 20°C and the solvent removed *in vacuo*. Purification by column chromatography on silica gel, eluting with 9:1 ethyl acetate:cyclohexane, gave the title compound as a pale yellow solid (0.8g).
LC/MS R_t 2.40 min, *m/z* 366 [MH^+]

Intermediate 7. 3-(Aminocarbonyl)-4-{[3-(methyloxy)phenyl]amino}-6-quinolinecarboxylic acid



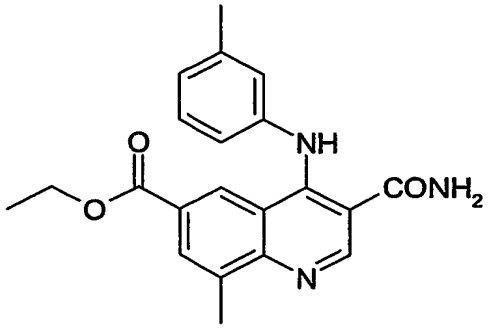
To a stirred solution of intermediate 6 (0.8g) in ethanol (25ml) was added 2M sodium hydroxide solution (15ml) and the mixture stirred at 20°C for 16h. The solvent was removed *in vacuo* and the residue dissolved in water (150ml) and washed with dichloromethane (100ml). The aqueous layer was acidified to pH4 by the addition of 2M hydrochloric acid and a precipitate formed which was collected by filtration to give the title compound as a yellow solid (460mg).
LC/MS R_t 1.93 min, *m/z* 338 [MH^+]

Intermediate 9. Ethyl 3-(aminocarbonyl)-4-chloro-8-methyl-6-quinolinecarboxylate



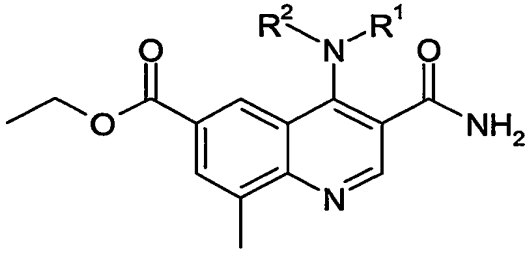
To a stirred solution of intermediate 8 (5g) in ethanol (100ml) was added palladium acetate (161mg). The flask was evacuated and refilled with nitrogen two times and then evacuated and refilled with carbon monoxide two times. The mixture was heated at 80°C under an atmosphere of carbon monoxide for 72h. The mixture was cooled to 20°C and the precipitate collected by filtration. The solid was suspended in dichloromethane (25ml) and methanol (25ml), loaded onto a 10g aminopropyl SPE ion exchange cartridge (Isolute, NH_2), and the cartridge was eluted with methanol. Evaporation of the solvent gave the title compound as a white solid (3g).
LC/MS R_t 2.85min, *m/z* 293 [MH^+]

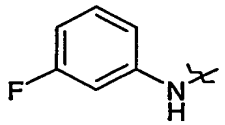
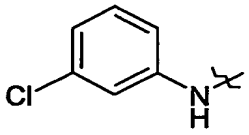
Intermediate 10. Ethyl 3-(aminocarbonyl)-8-methyl-4-[(3-methylphenyl)amino]-6-quinolinecarboxylate

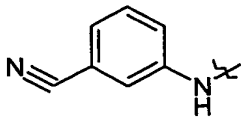
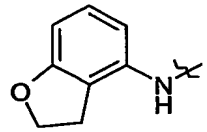
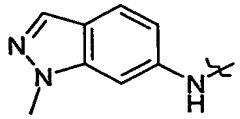
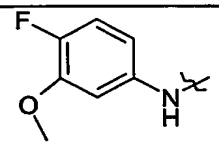
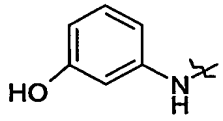


To a stirred suspension of intermediate 9 (50mg) in acetonitrile (3ml) was added 3-methylaniline (18mg; Aldrich) and the mixture heated at 80°C for 16h. The reaction was cooled to 20°C and the resultant precipitate was collected by filtration and dried *in vacuo* for 16h to give the title compound (55mg).
LC/MS R_t 2.62min, *m/z* 363 [MH^+]

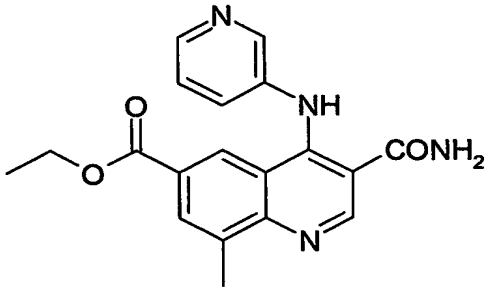
Similarly prepared from intermediate 9 were the following:



Intermediate Number	R^1R^2N-	Amine Reagent/ Source	LC/MS R_t (min)	LC/MS MH^+
11		3-Fluoroaniline / Aldrich	2.72	367
12		3-Chloroaniline / Aldrich	2.91	383

13		3-Aminobenzonitrile / Aldrich	2.67	374
14		2,3-Dihydro-1-benzofuran-4-amine / *Journal of Heterocyclic Chemistry* (1980), **17(6)**, 1333-5	2.55	391
15		1-Methyl-1*H*-indazol-6-amine / *Synthetic Communications* (1996), **26(13)**, 2443-2447	2.40	403
16		4-Fluoro-3-(methyloxy)aniline / Apollo-Chem	2.57	398
17		3-Aminophenol / Aldrich	2.3	366

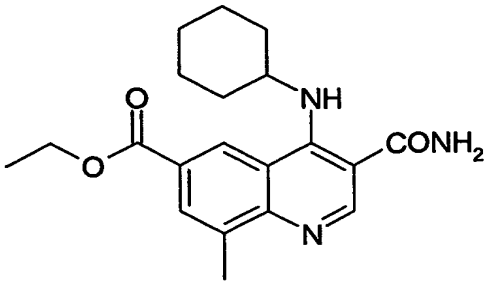
Intermediate 18. Ethyl 3-(aminocarbonyl)-8-methyl-4-(3-pyridinylamino)-6-quinolinecarboxylate



To a stirred suspension of intermediate 9 (50mg) in acetonitrile (3ml) was added pyridine hydrochloride (39.5mg) and 3-aminopyridine (16mg) (available from Aldrich). The mixture was heated at 80°C for 16h. The reaction was cooled to 20°C and the resultant precipitate was collected by filtration. Purification by mass directed preparative HPLC (Method A) gave the title compound (16mg).

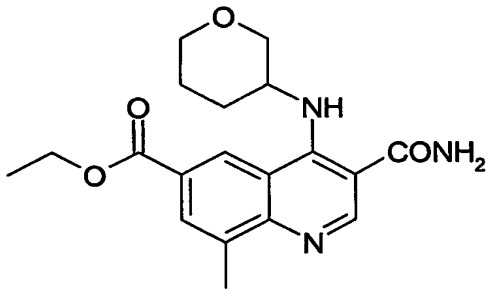
LC/MS R_t 2.14min, *m/z* 351 [MH^+]

Intermediate 19. Ethyl 3-(aminocarbonyl)-4-(cyclohexylamino)-8-methyl-6-quinolinecarboxylate



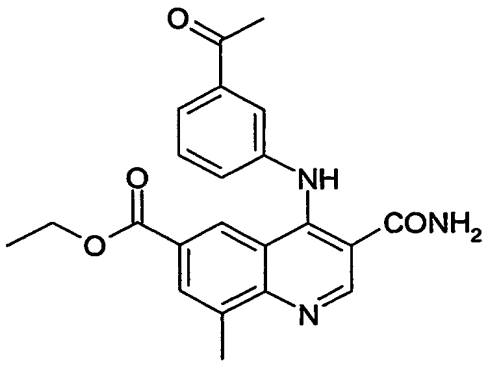
To a stirred suspension of intermediate 9 (50mg) in acetonitrile (3ml) was added cyclohexylamine (17mg) (available from Aldrich). The mixture was heated at 80°C for 16h. Further cyclohexylamine (17mg) was added and the mixture was heated at 80°C for 24h, then further cyclohexylamine (9mg) was added and the mixture was heated at 80°C for 74h. The reaction was cooled to 20°C and the resultant precipitate was collected by filtration and dried *in vacuo* to give the title compound (34mg).
LC/MS R_t 2.49min, *m/z* 356 [MH^+]

Intermediate 20. Ethyl 3-(aminocarbonyl)-8-methyl-4-(tetrahydro-2*H*-pyran-3-ylamino)-6-quinolinecarboxylate



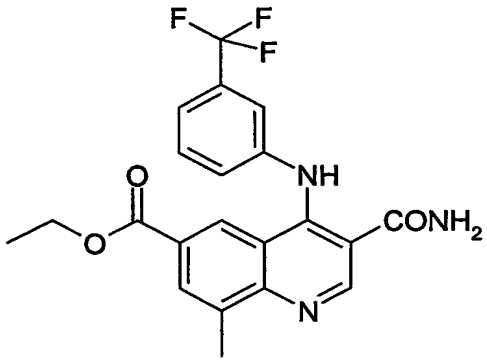
To a stirred suspension of intermediate 9 (50mg) in acetonitrile (3ml) was added tetrahydro-2*H*-pyran-3-amine (17mg; MicroChemistry Building Blocks). The mixture was heated at 80°C for 16h. Further tetrahydro-2*H*-pyran-3-amine (28mg) and N,N-diisopropylethylamine (46mg) were added and the mixture was heated at 80°C for 98h. The reaction was cooled to 20°C and the resultant precipitate was collected by filtration. The solid was dissolved in methanol and loaded onto a 10g sulphonic acid ion exchange cartridge (Isolute, SCX). The cartridge was washed with methanol and then eluted with 2M ammonia in methanol. Evaporation of the solvent gave the title compound (6mg).
LC/MS R_t 2.17min, *m/z* 358 [MH^+]

Intermediate 21. Ethyl 4-[(3-acetylphenyl)amino]-3-(aminocarbonyl)-8-methyl-6-quinolinecarboxylate



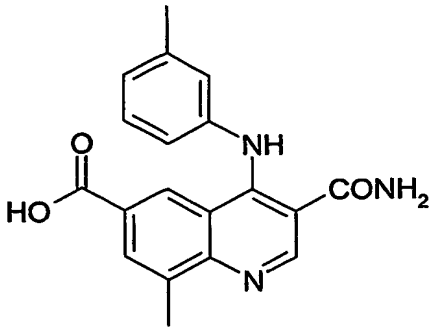
To a stirred suspension of intermediate 9 (50mg) in acetonitrile (3ml) was added 1-(3-aminophenyl)ethanone (23mg) (available from Aldrich). The mixture was heated at 80°C for 16h. Further 1-(3-aminophenyl)ethanone (6mg) was added and the mixture was heated at 80°C for 24h. The reaction was cooled to 20°C and the resultant precipitate was collected by filtration and dried *in vacuo* to give the title compound (71mg).
LC/MS R_t 2.46min, *m/z* 392 [MH^+]

Intermediate 22. Ethyl 3-(aminocarbonyl)-8-methyl-4-{[3-(trifluoromethyl)phenyl]amino}-6-quinolinecarboxylate



To a stirred suspension of intermediate 9 (50mg) in acetonitrile (3ml) was added 3-(trifluoromethyl)aniline (27mg) (available from Aldrich). The mixture was heated at 80°C for 16h. Further 3-(trifluoromethyl)aniline (7mg) was added and the mixture was heated at 80°C for 24h, then further 3-(trifluoromethyl)aniline (7mg) was added and the mixture was heated at 80°C for 74h. The reaction was cooled to 20°C and the resultant precipitate was collected by filtration and dried *in vacuo* to give the title compound (49mg).
LC/MS R_t 3.10min, *m/z* 418 [MH^+]

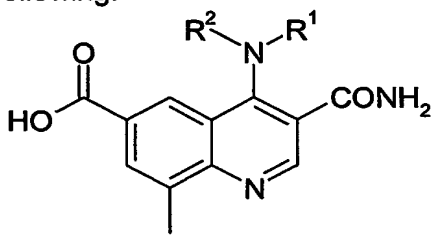
Intermediate 23. Ammonium 3-(aminocarbonyl)-8-methyl-4-[(3-methylphenyl)amino]-6-quinolinecarboxylate

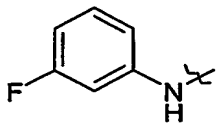
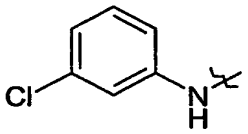
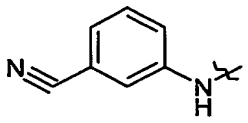
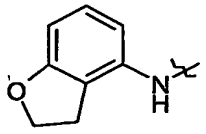


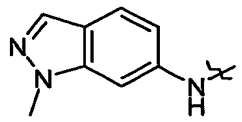
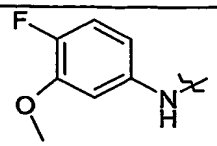
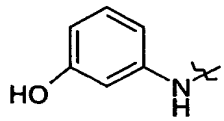
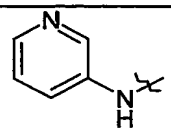
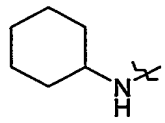
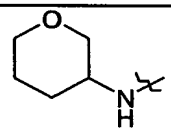
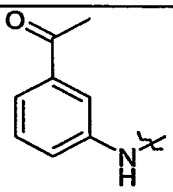
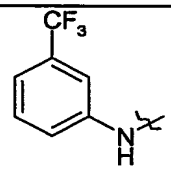
To a stirred solution of intermediate 10 (55mg) in tetrahydrofuran (2ml) and water (1ml) was added lithium hydroxide (3mg). The reaction was heated at 60°C for 16h. The mixture was cooled to 20°C and was loaded onto an aminopropyl SPE ion exchange cartridge (1g, Isolute), washed with methanol and eluted with 2M ammonia in methanol. The solvent was evaporated to give the title compound (31mg)

LC/MS R_t 3.10min, *m/z* 336 [MH^+]

Similarly prepared were the following:



Intermediate Number	R^1R^2N-	Starting Material	Isolation Method (a)	LC/MS R_t (min)	LC/MS MH^+
24		Intermediate 11	(I)	2.05	340
25		Intermediate 12	(I)	2.21	356
26		Intermediate 13	(II)	1.98	347
27		Intermediate 14	(I)	2.03	364

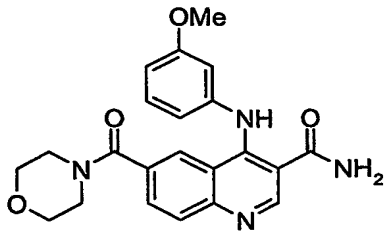
28		Intermediate 15	(I)	1.98	376
29		Intermediate 16	(I)	2.02	370
30		Intermediate 17	(I)	1.89	338
31		Intermediate 18	(I)	1.71	323
32		Intermediate 19	(II)	2.12	328
33		Intermediate 20	(I)	1.86	330
34		Intermediate 21	(II)	1.93	364
35		Intermediate 22	(II)	2.31	390

(a) Isolation Method:

(I) Purification by aminopropyl SPE ion exchange cartridge. Compounds isolated by this method are assumed to be ammonium salts.

(II) Purification by aminopropyl ion exchange cartridge followed by Mass Directed preparative HPLC (Method A). Compounds isolated by this method are assumed to be free carboxylic acids.

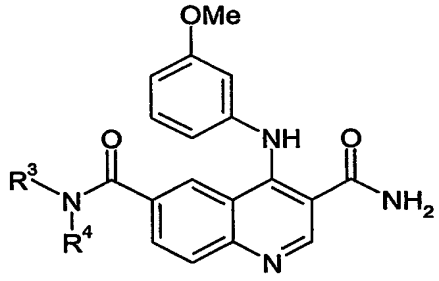
Example 1. 4-{[3-(Methyloxy)phenyl]amino}-6-(4-morpholinylcarbonyl)-3-quinolinecarboxamide

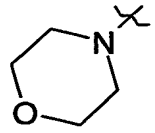
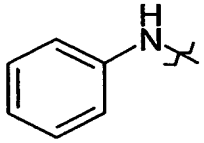


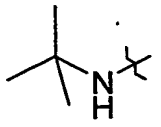
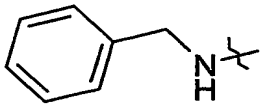
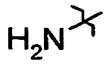
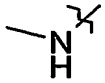
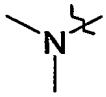
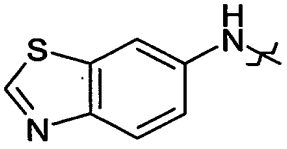
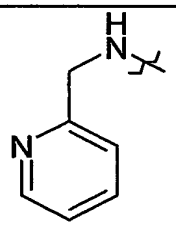
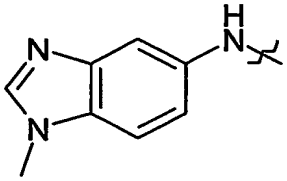
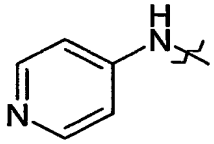
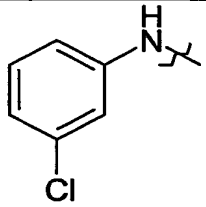
To a stirred solution of intermediate 7 (25mg) in *N,N*-dimethylformamide (3ml) was added 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (33mg) and the mixture stirred at 20°C for 30min. Morpholine (10mg) was added and the mixture stirred at 20°C for 16h. The solvent was removed under a flow of nitrogen. The residue was loaded onto a 1g SPE cartridge (aminopropyl stationary phase), washed with chloroform and eluted with 10% methanol in ethyl acetate. Concentration of the eluent and purification of the residue by mass directed HPLC gave the title compound as pale yellow solid (20mg).

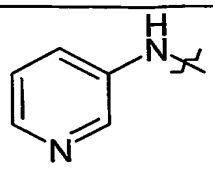
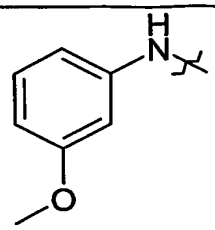
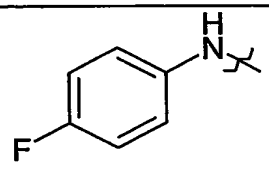
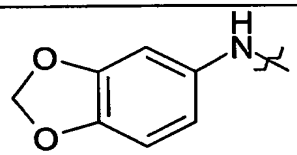
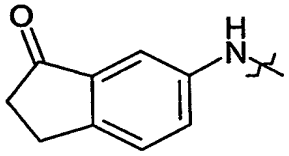
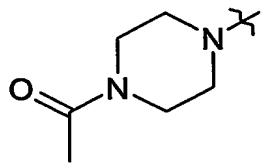
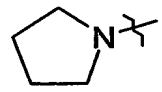
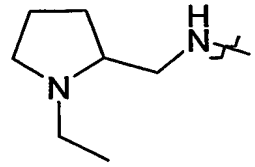
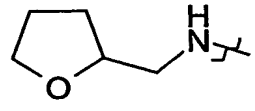
LC/MS R_t 2.05 min, *m/z* 407 [MH^+]

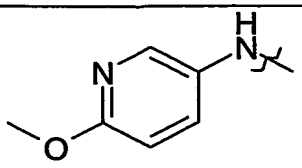
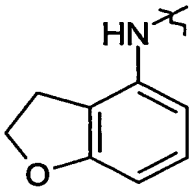
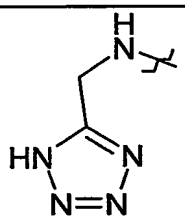
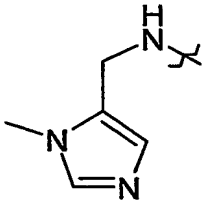
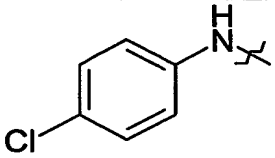
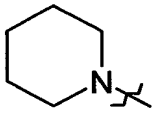
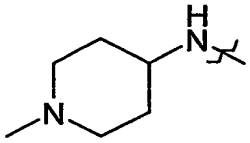
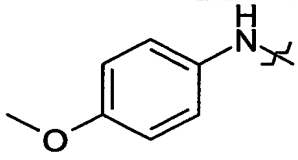
Similarly prepared from intermediate 7 were the following:

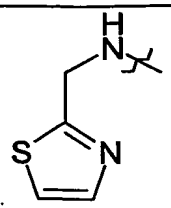
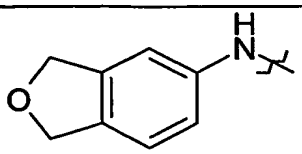
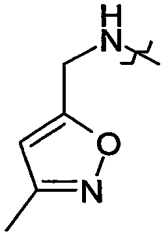
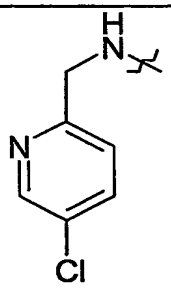


Example Number (a)	R^3R^4N-	Amine Reagent/ Source	Isolation Method (b)	LC/MS R_t (min)	LC/MS MH^+
1		Morpholine/ Aldrich	(I)	2.04	407
2		Aniline/ Aldrich	(I)	2.56	413

3		(1,1-Dimethylethyl)amine/ Aldrich	(I)	2.33	393
4		(Phenylmethyl)amine/ Aldrich	(I)	2.5	427
5		Ammonia/ Aldrich	(I)	1.8	337
6		Methylamine/ Aldrich	(I)	1.87	351
7		Dimethylamine/ Aldrich	(I)	1.93	365
8 TFA		1,3-Benzothiazol-6-amine/ Lancaster	(II)	2.66	470
9 TFA		(2-Pyridinylmethyl)amine/ Aldrich	(II)	2.23	428
10 TFA		1-Methyl-1H-benzimidazol-5-amine/ Heterocycles (1991), 32(5), 1003-12.	(II)	2.2	467
11 TFA		4-Pyridinamine/ Aldrich	(II)	2.11	414
12 TFA		3-Chloroaniline/ Aldrich	(II)	3.01	467

13 TFA		3-Pyridinamine/ Aldrich	(II)	2.28	414
14 TFA		3-(Methyloxy)aniline/ Aldrich	(II)	2.75	443
15 TFA		4-Fluoroaniline/ Aldrich	(II)	2.78	431
16 TFA		1,3-Benzodioxol-5- amine/ Aldrich	(II)	2.69	457
17 TFA		6-Amino-2,3-dihydro-1H- inden-1-one/ Journal of Medicinal Chemistry (2003), 46(3), 399-408.	(II)	2.66	467
18 TFA		1-Acetylpiperazine/ Aldrich	(II)	2.14	448
19 TFA		Pyrrolidine/ Aldrich	(II)	2.33	391
20 TFA		[(1-Ethyl-2- pyrrolidinyl)methyl]amine / Acros	(II)	1.99	448
21 TFA		(Tetrahydro-2- furanylmethyl)amine/ Aldrich	(II)	2.29	421

22 TFA		6-(Methyloxy)-3-pyridinamine/ Aldrich	(II)	2.66	444
23 TFA		2,3-Dihydro-1-benzofuran-4-amine/ Journal of Heterocyclic Chemistry (1980), 17(6), 1333-5.	(II)	2.67	455
24 TFA		(1H-Tetrazol-5-ylmethyl)amine Dynamit	(II)	2.12	419
25 TFA		[(1-Methyl-1H-imidazol-5-yl)methyl]amine/ WO0304467	(II)	1.91	431
26 TFA		4-Chloroaniline/ Aldrich	(II)	3	447
27 TFA		Piperidine/ Aldrich	(II)	2.45	405
28 TFA		1-Methyl-4-piperidinamine/ Journal of Medicinal Chemistry (1974), 17(1), 75-100	(II)	1.92	434
29 TFA		4-(Methyloxy)aniline/ Aldrich	(II)	2.68	443

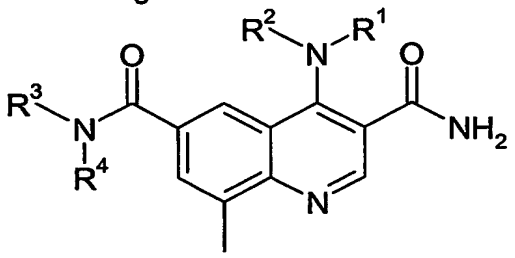
30 TFA		(1,3-Thiazol-2-ylmethyl)amine/ Tetrahedron (1995), 51(46), 12731-44	(II)	2.31	434
31 TFA		1,3-Dihydro-2-benzofuran-5-amine/ Journal of Medicinal Chemistry (1978), 21(9), 965-78	(II)	2.59	455
32 TFA		[(3-Methyl-5-isoxazolyl)methyl]amine/ Tetrahedron Letters (1993), 34(47), 7509-12	(II)	2.34	432
33 TFA		[(5-Chloro-2-pyridinyl)methyl]amine/ Journal of Organic Chemistry (1979), 44(3), 396-400	(II)	2.49	462

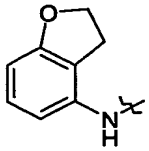
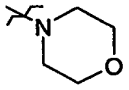
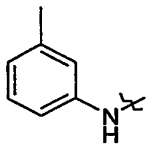
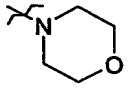
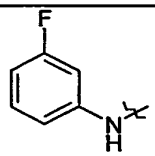
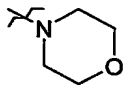
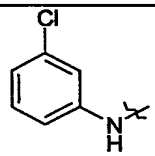
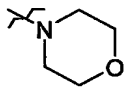
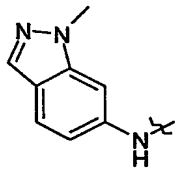
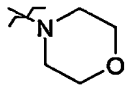
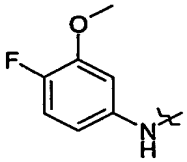
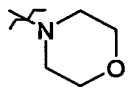
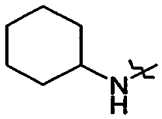
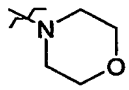
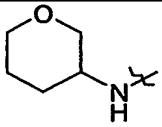
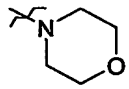
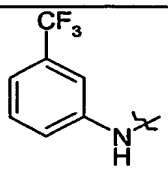
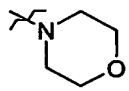
(a) Salt forms: TFA = trifluoroacetate salt

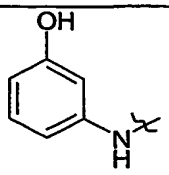
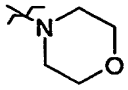
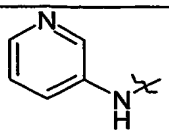
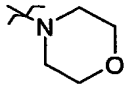
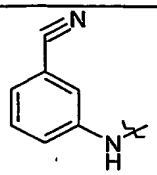
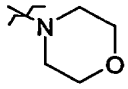
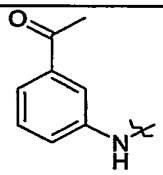
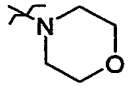
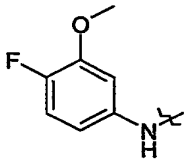
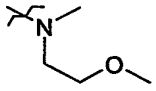
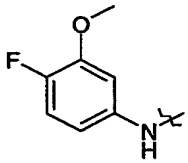
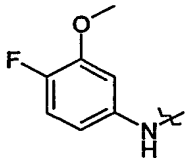
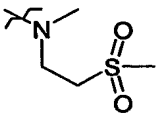
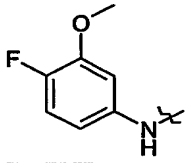
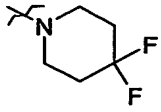
(b) Isolation Method: (I) Mass Directed HPLC Method A

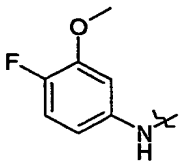
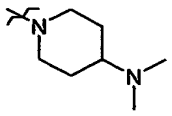
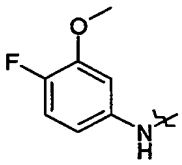
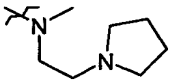
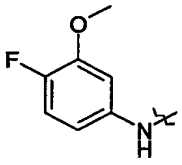
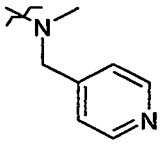
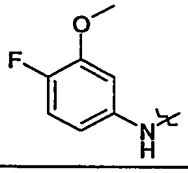
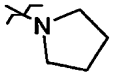
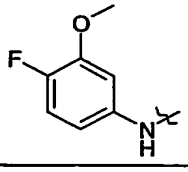
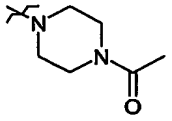
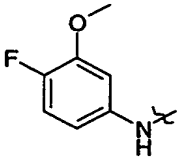
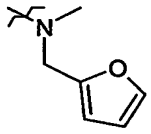
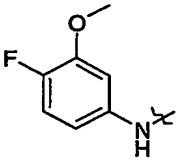
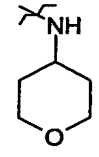
(II) Mass Directed HPLC Method B

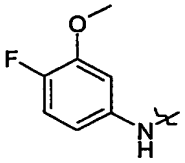
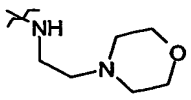
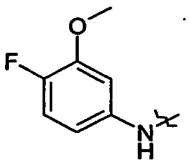
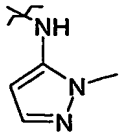
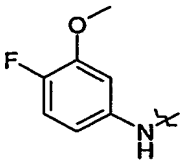
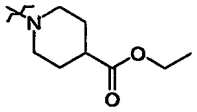
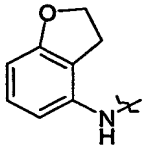
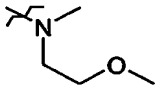
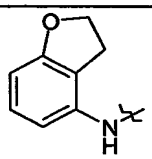
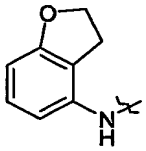
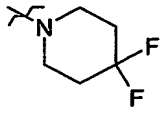
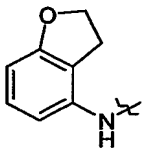
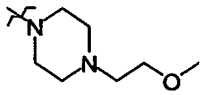
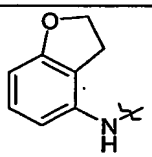
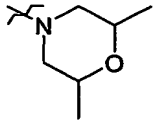
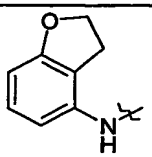
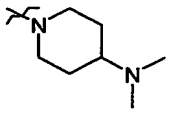
Similarly prepared were the following:

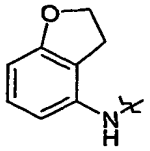
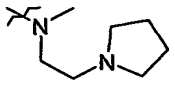
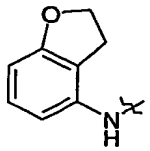
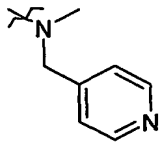
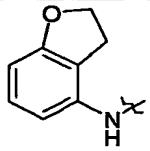
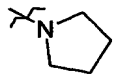
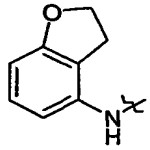
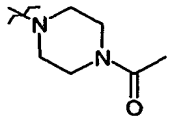
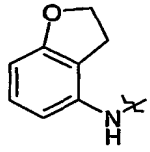
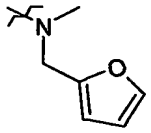
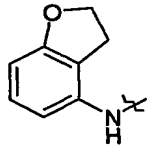
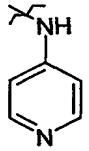
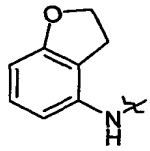
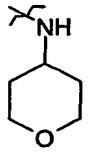


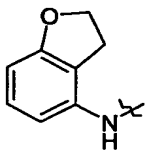
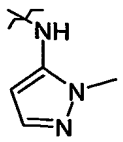
Example Number (a)	Starting Material	R^1R^2N-	R^3R^4N-	Amine Reagent/ Source	Isolation Method (b)	LC/MS R_t (min)	LC/MS MH^+
34	Intermediate 27			Morpholine / Aldrich	(I)	2.03	433
35	Intermediate 23			Morpholine / Aldrich	(I)	2.02	405
36	Intermediate 24			Morpholine / Aldrich	(I)	2.07	409
37	Intermediate 25			Morpholine / Aldrich	(I)	2.2	425
38	Intermediate 28			Morpholine / Aldrich	(I)	1.92	445
39	Intermediate 29			Morpholine / Aldrich	(I)	2.03	439
40	Intermediate 32			Morpholine / Aldrich	(I)	1.97	397
41	Intermediate 33			Morpholine / Aldrich	(II)	1.73	399
42	Intermediate 35			Morpholine / Aldrich	(II)	2.31	459

43	Intermediate 30			Morpholine / Aldrich	(II)	1.83	407
44	Intermediate 31			Morpholine / Aldrich	(II)	1.68	392
45	Intermediate 26			Morpholine / Aldrich	(I)	1.98	416
46	Intermediate 34			Morpholine / Aldrich	(II)	1.89	433
47	Intermediate 29			Methyl[2-(methyloxy) ethyl]amine / Fluorochem	(I)	1.93	441
48	Intermediate 29			Dimethyl amine / Aldrich	(II)	2.06	397
49	Intermediate 29			*N*-methyl-2-(methylsulphonyl) ethanamine / Array Biopharmma Inc	(I)	1.85	489
50	Intermediate 29			4,4-difluoro piperidine / Apollo	(I)	2.18	473

51 HCOOH	Intermediate 29			*N,N*-dimethyl-4-piperidinamine / Avocado Research Chemicals	(I)	1.71	480
52 HCOOH	Intermediate 29			*N*-methyl-2-(1-pyrrolidinyl) ethanamine / Micro Chemistry Building Blocks	(I)	1.77	480
53	Intermediate 29			Methyl(4-pyridinyl methyl) amine / Interchim Building Blocks	(I)	1.92	474
54	Intermediate 29			Pyrrolidine / Aldrich	(I)	2.03	423
55	Intermediate 29			1-Acetyl piperazine / Aldrich	(I)	1.86	480
56	Intermediate 29			(2-Furanyl methyl) methylamine / Aldrich	(I)	2.19	463
57	Intermediate 29			Tetrahydro-2*H*-pyran-4-amine / . Combi-Blocks Ltd	(I)	1.98	453

58 HCOOH	Intermediate 29			[2-(4-Morpholinyl) ethyl]amine / Aldrich	(I)	1.79	482
59	Intermediate 29			1-Methyl-1*H*-pyrazol-5-amine / Maybridge Chemical Co.	(I)	2.02	449
60	Intermediate 29			Ethyl 4-piperidine carboxylate / Aldrich	(I)	2.22	509
61	Intermediate 27			Methyl[2-(methyloxy) ethyl]amine / Fluorochem	(I)	1.95	435
62	Intermediate 27			Dimethyl amine / Aldrich	(II)	2.07	391
63	Intermediate 27			4,4-Difluoro piperidine / Apollo	(I)	2.2	467
64 HCOOH	Intermediate 27			1-[2-(Methyloxy) ethyl] piperazine / ABCR	(I)	1.78	490
65	Intermediate 27			2,6-dimethyl morpholine / ABCR	(I)	2.07	461
66 HCOOH	Intermediate 27			*N,N*-dimethyl-4-piperidin amine /	(I)	1.75	474

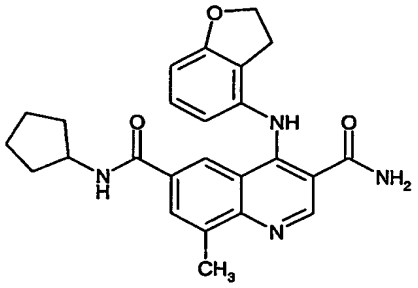
				Avocado Research Chemicals			
67 HCOOH	Intermediate 27			*N*-methyl-2-(1-pyrrolidinyl) ethanamine / Micro Chemistry Building Blocks	(I)	1.79	474
68	Intermediate 27			*N*-methyl-1-(4-pyridinyl)methanamine / Interchim Building Blocks	(I)	1.94	468
69	Intermediate 27			Pyrrolidine / Aldrich	(I)	2.03	417
70	Intermediate 27			1-acetyl piperazine / Aldrich	(I)	1.87	474
71	Intermediate 27			(2-Furanyl methyl) methylamine / Aldrich	(I)	2.17	457
72	Intermediate 27			4-Pyridinamine / Aldrich	(I)	2.01	440
73	Intermediate 27			Tetrahydro-2*H*-pyran-4-amine / Combi-Blocks Ltd	(I)	1.97	447

74	Intermediate 27			1-Methyl-1*H*-pyrazol-5-amine / Maybridge Chemical Co.	(I)	2	443

(a) Salt forms: HCOOH = formate salt

(b) Isolation Method: (I) Purification by aminopropyl SPE ion exchange cartridge followed by Mass Directed preparative HPLC (Method A)
(II) Purification by aminopropyl SPE ion exchange cartridge

Example 75. N^6-Cyclopentyl-4-(2,3-dihydro-1-benzofuran-4-ylamino)-8-methyl-3,6-quinolinedicarboxamide



To a stirred solution of intermediate 27 (20mg) in *N,N*-dimethylformamide (0.5ml) was added 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (16mg) followed by *N,N*-diisopropylethylamine (13mg). The mixture was stirred for 10 minutes, then cyclopentylamine (4.3mg; Aldrich) was added and the mixture was allowed to stand overnight. The solvent was blown off under a stream of nitrogen and the residue suspended in dimethylsulphoxide:methanol (1:1; 1ml). The undissolved solid was collected by decanting off the liquid. Purification of the solid by Mass Directed preparative HPLC (Method A) gave the title compound as a white solid (10mg). LC/MS R_t 2.5 min, *m/z* 431 [MH^+].